

From: Eassa, Samar (HC/SC)
Sent: 2021-06-17 3:57 PM
To: Bouthillier, Leo (HC/SC); Blahoianu, Maria (HC/SC)
Cc: Alhaddad, Saj (HC/SC); Hunt, Melissa (HC/SC); Rose, Jhona (HC/SC); Stothart, Tonja (HC/SC); Panetta, Vincent (HC/SC); Salem, Myriam (HC/SC)
Subject: RE: *tentative* Meeting to Discuss Pfizer COVID-19 vaccine Product Monograph
Attachments: Response to MHPD request of Jun-07-2021 (PDF).pdf

Hello Leo and Maria,

As a background on the invite below for the meeting with Pfizer, please note the following:

1. **This is a MHPD Lead informal discussion**, extended to BRDD since Pfizer requested a short call with BRRD/MHPD to discuss upcoming revisions to the Product Monograph for Pfizer-BioNTech COVID-19 Vaccine (COMIRNATY). This comes as a follow up on their pre-NDS meeting control # 253345 held on June 3, 2021 and further to the response to the MHPDs request of 7 Jun 2021, under PSUR control # 253419: [HC6-024-e243022 \(0133\) Biologic Dossier](#) (response document attached)
2. **The purpose of this meeting** is to discuss the need to update the PM to include the identified safety issues. MHPD has outlined a number of post market safety signals (Adverse Events) related to Pfizer-BioNTech COVID-19 Vaccine (COMIRNATY) for Pfizer's consideration for update in the PM.
Please refer to the attached document for MHPD comments and Pfizer response.
3. **The next planned PM update** for Pfizer-BioNTech COVID-19 Vaccine (COMIRNATY) is communicated to be submitted under the rolling sequence #2 of Pfizer NDS CV, control # 252736, planned for July 16, 2021.
4. **Please advise** if you would like to extend the invite to further attendees/reviewers from the BRDD side, to be present in this informal discussion about the PM.

Best regards,
Samar

-----Original Appointment-----

From: Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>
Sent: 2021-06-17 9:28 AM
To: Alhaddad, Saj (HC/SC); Hunt, Melissa (HC/SC); Rose, Jhona (HC/SC); Stothart, Tonja (HC/SC); Bouthillier, Leo (HC/SC); Blahoianu, Maria (HC/SC); Eassa, Samar (HC/SC); Panetta, Vincent (HC/SC); Salem, Myriam (HC/SC)
Subject: *tentative* Meeting to Discuss Pfizer COVID-19 vaccine Product Monograph

When: 2021-06-21 11:30 AM-12:00 PM (UTC-05:00) Eastern Time (US & Canada).

Where: TBD

In accordance with the Risk Management Plan Terms and Conditions, imposed under the Interim Order Respecting the Importation, Sale and Advertising of Drugs for Use in Relation to Covid-19, Pfizer Canada ULC is required to submit monthly safety reports for the period of the Interim Order authorization. As such, you are requested to submit the monthly safety report for the period of April 30, 2021 to May 31, 2021 including cumulative number of reports (serious and non-serious) and adverse events that occurred in Canada and globally for the Pfizer-BioNTech COVID-19 Vaccine (tozinameran) known to Pfizer Canada ULC and BioNTech Manufacturing GmbH.

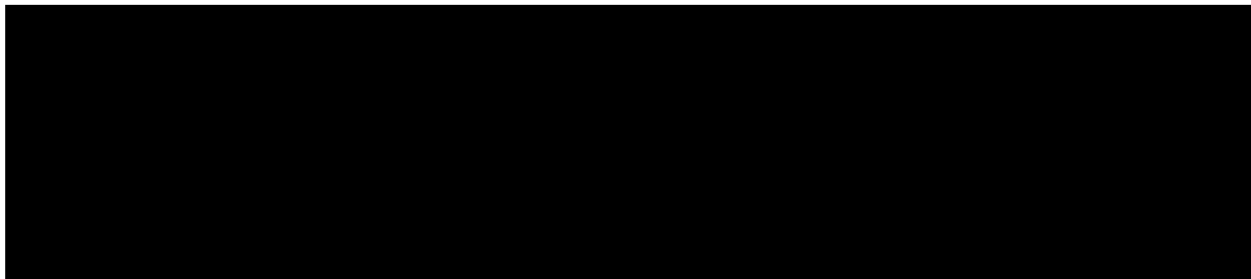
Actions for Pfizer Canada ULC and BioNTech Manufacturing GmbH stemming from the SMSR #5 review are to:

Comment 1

Discuss the need to submit a new Post-Authorization change – PM safety update and/or update the risk management plan regarding the following risks:

- a. Facial paralysis /Bell's Palsy in association with the Pfizer-BioNTech COVID-19 Vaccine, based on the imbalance observed in the clinical trials, increase in frequency of reporting from the post-market data, and safety information captured in the EMASmPC and EUA USPI (including Bell's Palsy).*
- b. Myocarditis/Pericarditis in association with the Pfizer-BioNTech COVID-19 Vaccine-based on the following:*
 - substantive number of cases that met the Bonaca criteria for definite, probable and possible myocarditis in the SMSR #5*
 - most events are temporally related to the vaccination*
 - Israel Ministry of Health¹ concluded a possible link between the second dose and the onset of myocarditis among young men (16-30), and that this link was highlighted to be stronger among the 16-19 younger age group.*
 - that adolescents and the young adult population will soon be vaccinated in much larger numbers.*

Response 1:



Comment 2

Discuss the timeline for alignment of the Reference Safety Information and the Canadian Product Monograph for the following events: Asthenia, Lethargy, Decreased appetite, Hyperhidrosis, Night sweats and Paresthesia. In addition, address any plans to include labelling updates from other jurisdictions, such as facial swelling in people with a history of injections with dermal fillers recommended by the European Medicines Agency.

Response 2:**Comment 3**

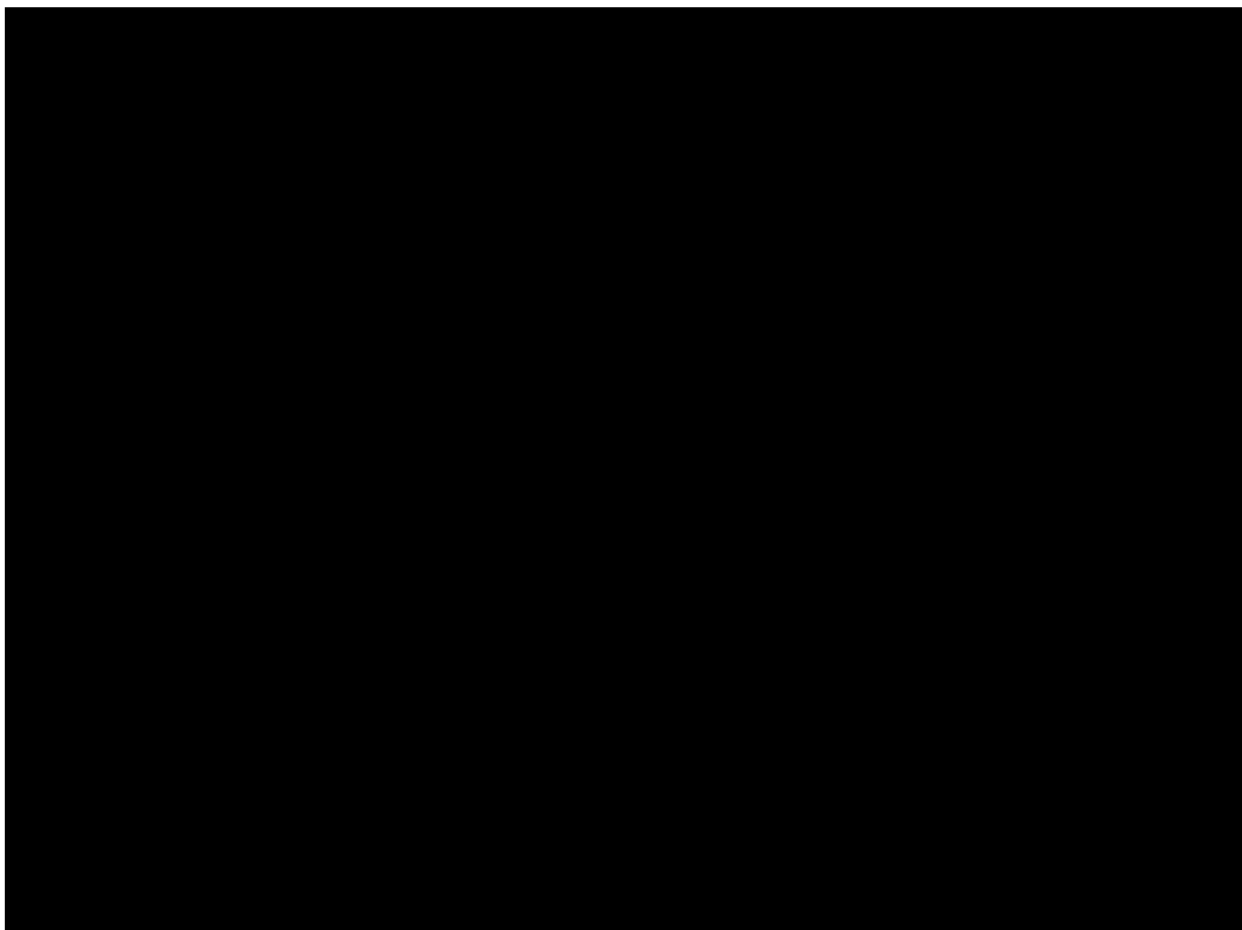
In addition, please include the following in the next SMSR:

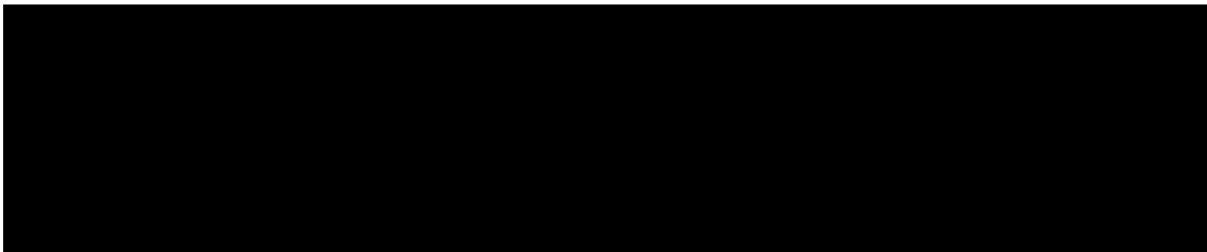
Provide an updated cumulative review of the following safety topics. Data should be stratified by sex, age, gender, dose 1 or dose 2 and assessed for causality using Brighton Collaboration Definition Criteria (or validated Definition Criteria). The observed and expected analyses should be included. An analysis of Canadian cases should be included. In addition, discuss the need for any potential amendment to the product monograph

and/or the risk management plan and make, accordingly, a proposal for the changes to the relevant sections within this discussion.

- a. Cases of thrombosis with thrombocytopenia following vaccination with Pfizer BioNtech using appropriate SMQs to extract the cases including: thrombotic events with/without thrombocytopenia and thrombocytopenia without applying time limit specifications.*
- b. Cases of seizure following vaccination of Pfizer BioNtech vaccine. Search criteria should be included and encompass all generalized convulsive seizures following immunization.*
- c. Cases of hypertensive crisis with intracranial haemorrhage and provide a discussion regarding cases recently described in the literature.*
- d. Cases of hearing loss and trigeminal neuralgia, and provide a discussion regarding cases recently analyzed.*

Response 3:







Pfizer Canada

Affaires réglementaires / Regulatory Affairs

17300, autoroute Transcanadienne, Kirkland (Québec) H9J 2M5

17300 Trans-Canada Highway, Kirkland, QC H9J 2M5

14 June 2021

CONFIDENTIAL

Melissa Hunt, Director
Marketed Health Products Directorate (MHPD)
Address Locator # 1906A
OTTAWA, Ontario
K1A 0K9

**Attention: Saj Alhaddad Acting Senior Regulatory Project Manager
Bureau of Biologics, Radiopharmaceuticals and Self-Care Products, MHPD**

**Subject: Pfizer-BioNTech COVID-19 Vaccine
COVID Interim Order Application (COV19)
Fulfilling Terms and Conditions-Risk Management Plan Condition no.2**

**Reference: Dossier ID HC6-024-e243022; Control No. 253419
Sequence 0133 (Related sequences 0054, 0072, 0089, 100, 116 and 0122)**

Dear Mr. Alhaddad,

Reference is made to the COVID Interim Order Application for Pfizer-BioNTech COVID-19 Vaccine for which a Notice of Authorization was issued on 9 December 2020. Please find attached the sixth Summary Monthly Safety Report-SMSR (dated 13 June 2021) for PF-07302048 (Pfizer-BioNTech COVID-19 Vaccine), covering the period from 30 April 2021 through 31 May 2021. The filing of this SMSR meets the monthly requirement per the Terms and Conditions-RMP Condition no.2. In addition, please also find the responses to the MHPD's request dated 7 June 2021 (copy enclosed).

The information supplied herewith is considered to be confidential and covered under section 20(1) of the *Access to Information Act*. Notice of any request for access to this information, or any part thereof, is to be given in writing to:

Pfizer Canada ULC
17300 Trans-Canada Highway, Kirkland, Quebec H9J 2M5
Attention: Director, Regulatory Affairs

For all technical e-CTD queries, please submit your request via email to eSubmissions-CA@pfizer.com or communicate via fax to (514) 426-6824.

We trust that you will find this information to your satisfaction. Should you require additional information, please do not hesitate to contact me at [REDACTED] or [REDACTED] at [REDACTED]. Alternatively, you may reach us by fax at (514) 426-6824.

Sincerely,

[REDACTED]

([REDACTED] for)

[REDACTED]
Regulatory Affairs
Pfizer Canada ULC

pfizer.ca



Health Santé
Canada Canada

**Health Products and Food Branch
Direction générale des produits de santé et des aliments**

Marketed Health Products Directorate	The Marketed Health Products Directorate (MHPD) is responsible for coordination of consistency of post-market surveillance and assessment of signals and safety trends concerning all marketed health products.
Direction des produits de santé commercialisés	La Direction des produits de santé commercialisés (DPSC) est chargée de la coordination et la cohérence des activités de surveillance post-approbation et d'évaluer les signaux et les tendances concernant l'innocuité de tous les produits de santé commercialisés.

MEMORANDUM

NOTE DE SERVICE

TO : Director
À Centre for Evaluation of
Radiopharmaceuticals and
Biotherapeutics (CERB)
Biologic and Radiopharmaceutical
Drugs Directorate (BRDD)

FROM : Director
DE Bureau of Biologics,
Radiopharmaceuticals and Self-Care
Products (BBRS)
Marketed Health Products
Directorate (MHPD)

SECURITY - CLASSIFICATION - DE SÉCURITÉ

OUR FILE - NOTRE RÉFÉRENCE

SAP # 3013445

YOUR FILE - VOTRE RÉFÉRENCE

DATE

September 11, 2021

SUBJECT : Ad-Hoc report on myocarditis/pericarditis and messenger ribonucleic
OBJET acid (mRNA) COVID-19 Vaccines

- ☒ No Action Required—FYI Only
- ☐ Recommended For Immediate Action
- ☐ Recommended For Action Post Approval/at Next Opportunity

The Bureau of Biologics, Radiopharmaceuticals and Self-Care Products (BBRS) of the Marketed Health Products Directorate (MHPD) has completed an Ad-hoc review on myocarditis/pericarditis following vaccination with mRNA COVID-19 Vaccines. The purpose of this review was to formalize the assessment on the risk of myocarditis/pericarditis events with the mRNA Vaccines (PFIZER-BIONTECH COVID-19 VACCINE and COVID-19 Vaccine Moderna), to summarize the regulatory actions taken thus far, and to determine the need for additional regulatory steps.

The review of all of the information provided by MAHs and international partners (under confidentiality agreement) suggested that the benefits of the COVID-19 mRNA vaccines in preventing COVID-19 outweigh the risk of events of myocarditis/pericarditis. This is based on the following:

- Cases of myocarditis and/or pericarditis following immunization with COVID-19 vaccines have been reported in a small number of people in Canada and internationally. These reports are very rare. Health Canada and other international regulators are continuing to investigate the potential relationship between COVID-19 vaccines and these rare events.
- Most reported cases to date have followed vaccination with an mRNA vaccine based on an analysis of international cases, have occurred more often after the second dose and in younger male adults and adolescents. The Canadian evidence is expected to evolve as more people in these populations are vaccinated.
- Myocarditis/pericarditis following vaccination with an mRNA vaccine is mostly mild to moderate in severity, however severe and fatal cases can occur. The actual incidence is difficult to determine. Timely diagnosis and treatment may improve a patient's prognosis.
- Myocarditis/pericarditis following vaccination with mRNA vaccines was shown to resolve quickly with proper treatment; however, long-term sequelae in these cases is unknown. Tight follow-up and timely treatment may minimize this risk.
- This risk and the labelling changes have been communicated to the Canadian public through Infowatch and a public advisory.

Our review noted that there are remaining knowledge gaps including the exact mechanism of action of the myocarditis/pericarditis following vaccination and risk factors for risk minimization. In addition, available short-term follow-up data show that these events were typically mild and treatable; however, information on long-term outcomes is not yet available.

Memorandum

-2-

Document Released Under the Access to Information

For your information, a copy of this review is available in the docubridge with the same control number.

No further action to BRDD at this time.

This document has been signed electronically using the Health Canada docuBridge system. /
Ce document a été signé électroniquement à l'aide du système docuBridge de Santé Canada.

Marketed Health Products Directorate
Direction des produits de santé commercialisés

Ad-Hoc Report

messenger ribonucleic acid (mRNA) COVID-19 Vaccines

**PFIZER-BIONTECH COVID-19 VACCINE and COVID-19 Vaccine
Moderna**

Myocarditis/Pericarditis

SAP #3013445

Position Title: Director / Directeur(ice)
Bureau: Bureau of Biologics, Radiopharmaceuticals and Self-Care Products/ Bureau des produits biologiques, radiopharmaceutiques et auto-administratifs
Date: July 29, 2021
Signature: <i>This document has been signed electronically using the Health Canada docuBridge system.</i> / Ce document a été signé électroniquement à l'aide du système docuBridge de Santé Canada
Security – Classification – de sécurité: Protected B when completed / protégé B une fois terminé

MHPD – PROTECTED B**REVIEW REPORT**

Title: Review Report: messenger ribonucleic acid (mRNA) COVID 19 Vaccines
 PFIZER-BIONTECH COVID-19 VACCINE and COVID-19 Vaccine Moderna and
 Myocarditis/Pericarditis

Date: July 29, 2021

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Caveat: This document includes

-International confidential information shared under a Memorandum Of Understanding (MOU), confidential information is identified throughout the document (highlighted).

*-Verbatim excerpts from **director-approved reviews prior to the labelling the risk of myocarditis/pericarditis**. Historical excerpts are italicised throughout the document (e.g. excerpts from Monthly Safety Reports reviews under Section 6.1.2)*

MHPD – PROTECTED B

REVIEW REPORT

1. Issue:

On March 3, 2021, cases of myocarditis following vaccination with the PFIZER-BIONTECH COVID-19 VACCINE were first discussed at the international regulatory meeting, Pharmacovigilance Cluster, under the confidentiality agreement. The European Medicines Agency (EMA) discussed the information they received from the Israeli Ministry of Health regarding their investigation on a safety signal of myocarditis/pericarditis in younger population (16-30 years of age) following vaccination with the PFIZER-BIONTECH COVID-19 VACCINE. At the time, the Israeli Ministry of Health had received 40 cases appearing adjacent to the administration of the vaccine. All participating regulatory members including the European Medicines Agency (EMA), the U.S. Food Drugs Administration (FDA), the Medicines and Healthcare product Regulatory Agency (MHRA), the Japan Pharmaceuticals and Medical Devices Agency (PMDA) and Health Canada were in agreement that, at that time, the risk of myocarditis/pericarditis was not yet a safety signal and would continue to be monitored closely. Following this meeting, myocarditis/pericarditis continued to be discussed at different international regulatory meetings including, but not limited to, the International Coalition of Medicines Regulatory Authorities (ICMRA) meetings for COVID-19 Vaccine.

In early May¹, the EMA Pharmacovigilance Risk Assessment Committee (PRAC) requested marketing authorization holders (MAH) of COVID-19 messenger ribonucleic acid (mRNA) vaccines (BioNTech Manufacturing GmbH and ModernaTX, Inc.) to provide a detailed analysis of myocarditis and pericarditis events due to an increase in reporting of these events.

On May 24, 2021, the Advisory Committee on Immunization Practices (ACIP) COVID-19 Vaccine Safety Technical (VaST) Work Group of the Centers for Disease Control and Prevention (CDC) reviewed the data on myocarditis and pericarditis² following the COVID-19 vaccination with an mRNA vaccine. Data from the Vaccine Adverse Reporting System (VAERS) showed a higher number of observed than expected on the cases of myocarditis and pericarditis in age 16 to 24 year olds within the 30-day window following the second dose of COVID-19 mRNA vaccination. However, this result was not seen in data from Vaccine Safety Datalink (VSD). It was recommended to continue monitoring the data for potential cases of myocarditis/pericarditis following vaccination with mRNA vaccines and to provide information to clinicians to enhance recognition and management.

On June 01, 2021, Israel publicly shared the result of their analyses that the incidence rate of myocarditis in young male following vaccination was higher than the background rate. The

¹ <https://www.ema.europa.eu/en/news/meeting-highlights-pharmacovigilance-risk-assessment-committee-prac-3-6-may-2021>

² COVID-19 VaST Technical Report May 24, 2021 | CDC

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Israeli Ministry of Health³ concluded a possible link to myocarditis and pericarditis⁴. This link was found to be stronger among the younger age group of 16 to 19 years of age, compared to other age groups.

On June 23-25, 2021, another ACIP meeting was held where it was concluded⁵ that the occurrence of myocarditis after mRNA COVID-19 vaccines was commonly seen in males under 30 years of age, within a few days after the second dose. The highest reporting rates were among males aged 12 to 17 years⁶. Following the ACIP meeting on June 25, 2021, Health Canada was informed via confidential agreement that the US Prescribing Information (USPI) for PFIZER-BIONTECH COVID-19 VACCINE would be updated to reflect the risk of myocarditis and pericarditis following administration of this vaccine. On June 25, a courtesy copy of the draft USPI was shared by the FDA with Health Canada. Similarly on the same day, the MHRA updated their labelling for COVID-19 Vaccine Moderna on myocarditis and pericarditis.

On the same date, Health Canada issued an advisement letter to both mRNA vaccine MAHs (Pfizer Canada ULC, HC6-024-e243022 (1.0) Reg Info - Health Product (DSTS control # 254161) and ModernaTX, Inc. HC6-024-e244946 (1.0) Reg Info - Health Product (DSTS control #254172) requesting the inclusion of the risk of myocarditis and pericarditis following vaccination with PFIZER-BIONTECH COVID-19 VACCINE or COVID-19 Vaccine Moderna. The Canadian Product Monographs (CPMs) were updated on June 30, 2021 with these events.

The Marketed Health Product Directorate (MHPD) initiated this Ad-hoc review on myocarditis and pericarditis in early June 2021 following the assessment of the 5th monthly safety report for the PFIZER-BIONTECH COVID-19 VACCINE (covering the month of April; Control # 251813) and 4th monthly safety report for COVID-19 Vaccine Moderna (covering the month of April; Control #252740). Following these reviews, Health Canada requested the MAHs to provide additional data and to update the Risk Management Plans (RMPs) with myocarditis/pericarditis as an important potential risk^{7,8}.

2. Purpose:

The purpose of this review is

³ Surveillance of Myocarditis (Inflammation of the Heart Muscle) Cases Between December 2020 and May 2021 (Including) | Ministry of Health (www.gov.il)

⁴ <https://www.gov.il/en/departments/news/01062021-03>

⁵ Overview of Myocarditis and Pericarditis (cdc.gov)

⁶ Use of mRNA COVID-19 Vaccine After Reports of Myocarditis Among Vaccine Recipients: Update from the Advisory Committee on Immunization Practices — United States, June 2021 | MMWR (cdc.gov)

⁷ HC6-024-e243022 (1.0) Reg Info - Post Market Tracker

⁸ HC6-024-e244946 (1.0) Reg Info - Post Market Tracker

MHPD – PROTECTED B**REVIEW REPORT**

- to formalize the assessment of the risk of myocarditis and/or pericarditis following vaccination with an mRNA COVID-19
- to summarize the regulatory actions taken thus far, and
- to determine the need for additional regulatory actions.

3. Background:

3.1 Product classification and Indications

3.1.1 Canada

At the time of this review, there are currently two (2) COVID-19 mRNA vaccines authorized in Canada under the *Interim Order Respecting the Importation, Sale and Advertising of Drugs for Use in Relation to COVID-19* (ISAD IO):

- 1) PFIZER-BIONTECH COVID-19 VACCINE; Authorized on December 9, 2020 (Control # 244906) for *active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS- CoV-2) in individuals 16 years of age and older.*

On May 5, 2021, Health Canada issued an interim authorization to expand the indication of this vaccine to individuals aged 12-15 years (Control #251730). As of that date, the Pfizer-BioNTech COVID-19 Vaccine is indicated for:

“Active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 12 years of age and older.”

- 2) COVID-19 Vaccine Moderna: Authorized on December 23, 2020 (control #244946) for *active immunization against coronavirus disease 2019 (COVID-19) caused by the SARS-CoV-2 virus in individuals 18 years of age and older.* The pediatric indication for individuals aged 12 to 17 years is under review.

3.1.2 European Medicines Agency

In the European Union (EU), at the time of this review:

- PFIZER-BIONTECH COVID-19 VACCINE (referred to as *Comirnaty*⁹) indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus in 12 years and above

⁹ https://www.ema.europa.eu/en/documents/product-information/comirnaty-epar-product-information_en.pdf

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- COVID-19 Vaccine Moderna (referred to as *Spikevax*¹⁰) indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus in 18 years and above

On July 23, 2021, the EMA's Committee for Medicinal Products for Human use (CHMP) recommended granting the extension of indication for the COVID-19 vaccine Spikevax to include use in children aged 12 to 17 years.¹¹

3.1.3 Food and Drug Administration (FDA)

In the United States, at the time of this review the PFIZER-BIONTECH COVID-19 VACCINE and COVID-19 Vaccine Moderna were granted an Emergency Use Authorization (EUA) to permit the emergency use for active immunization to prevent COVID-19 with similar age indication for use as in Canada and EU.

3.1.4 Israel

In Israel, at the time of this review the PFIZER-BIONTECH COVID-19 VACCINE is the only vaccine authorized for use in individuals 12 years of age and older.

3.1.5 Medicines and Healthcare products Regulatory Agency (MHRA)

In the United Kingdom (UK), at the time of this review the PFIZER-BIONTECH COVID-19 VACCINE is the only vaccine authorized for use in individuals 12 years of age and older to prevent COVID-19 disease caused by SARS-CoV-2 virus¹².

3.1.6 Therapeutic Goods Administration (TGA)

In Australia, at the time of this review the PFIZER-BIONTECH COVID-19 VACCINE is currently indicated for active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV2, in individuals 16 years of age and older¹³.

Of note, the TGA granted a *provisional determination* to Pfizer Australia allowing the MAH to apply to *vary its provisional registration for the vaccine for use in individuals 12 years of age and older*¹⁴.

MHPD comments:

¹⁰ <https://www.ema.europa.eu/en/medicines/human/EPAR/spikevax-previously-covid-19-vaccine-moderna>

¹¹ <https://www.ema.europa.eu/en/news/covid-19-vaccine-spikevax-approved-children-aged-12-17-eu>

¹² [Information for Healthcare Professionals on COVID-19 Vaccine Pfizer/BioNTech \(Regulation 174\) Updated July 09, 2021](#)

¹³ [AUSTRALIAN PRODUCT INFORMATION –COMIRNATY™ \(BNT162b2 \[mRNA\]\) COVID-19](#)

¹⁴ [Provisional determination granted to Pfizer in relation to COVID 19 vaccine, COMIRNATY - for use in individuals 12 years of age and older](#)

MHPD – PROTECTED B**REVIEW REPORT**

The PFIZER-BIONTECH COVID-19 VACCINE is the only mRNA vaccine that is currently approved for use in the adolescent population (age 12 years and older). In Canada, the National Advisory Committee on Immunization (NACI)¹⁵ has recommended a complete series (two doses) of PFIZER-BIONTECH COVID-19 VACCINE in 12 years and older.

In EU, the recommendation of use of the PFIZER-BIONTECH COVID-19 VACCINE in adolescents differ across EU member states.

The Netherlands

On June 9, 2021, the Dutch Health Council gave a positive recommendation to begin vaccinating children aged 12 to 15 years¹⁶ who are vulnerable to serious symptoms of the coronavirus disease in addition to those aged 16 and 17 years from high-risk groups¹⁷.

Germany

On June 10, 2021, the German vaccine advisory committee, the Standing Committee on vaccination (STIKO), gave limited approval for the pediatric indication¹⁸. As per the panel statement¹⁹ : *it was not currently recommending the use of the vaccine for those aged 12-17 years without pre-existing conditions, although noted doctors were allowed to give the shot if the individual accepts the risk*. An updated version of the national immunization schedule is expected to be published in August in the Epidemiological Bulletin of the Robert Koch Institute²⁰.

United Kingdom (UK)

On June 16, 2021, news reports^{21,22} suggested that the Joint Committee on Vaccination and Immunisation (JCVI) will not advise the Government to press ahead with a vaccination campaign for under 18 years of age.

¹⁵ National Advisory Committee on Immunization

¹⁶ Netherlands-will-give-covid-vaccines-medically-vulnerable-adolescents

¹⁷ Covid-vaccination-starts-16-18-year-olds-high-risk-groups

¹⁸ Vaccine for children in Germany: Recommendation to vaccinate 12-17 year olds with underlying diseases - World Stock Market

¹⁹ <https://www.euronews.com/2021/06/10/us-health-coronavirus-germany-biontech>

²⁰ RKI - STIKO Recommendations

²¹ JCVI-not-recommending-vaccinating-children

²² Vaccination-experts-are-not-recommending-covid-jabs-for-under-18s-says-cabinet-minister

MHPD – PROTECTED B**REVIEW REPORT****3.2. Product characteristics****3.2.1 PFIZER-BIONTECH COVID-19 VACCINE**

The nucleoside-modified mRNA in the PFIZER-BIONTECH COVID-19 VACCINE is formulated in lipid nanoparticles, which enable delivery of the non-replicating mRNA into the host's cells to allow expression of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike antigen²³. The mRNA codes for membrane-anchored, full-length Spike (S) with two point mutations within the central helix. Mutation of these two amino acids to proline locks S in an antigenically preferred prefusion conformation²⁴. The protection against COVID-19 disease may be attributed to both the neutralizing antibody and immune cellular responses to the spike antigen²⁵.

Each dose of the PFIZER-BIONTECH COVID-19 VACCINE contains 30 µg of mRNA in a 0.3 mL suspension. Each dose of the PFIZER-BIONTECH COVID-19 VACCINE also includes the following ingredients: lipids (■■■■ mg (4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), ■■■■ mg 2[(polyethylene glycol)-2000]- N,N-ditetradecylacetamide, ■■■■ mg 1,2-distearoyl-sn-glycero-3-phosphocholine, and ■■■■ mg cholesterol), ■■■■ mg potassium chloride, ■■■■ mg monobasic potassium phosphate, ■■■■ mg sodium chloride, ■■■■ mg dibasic sodium phosphate dihydrate, and ■■■■ mg sucrose. The diluent (0.9% Sodium Chloride Injection, USP) contributes an additional ■■■■ mg sodium chloride per dose.

3.2.2 COVID-19 Vaccine Moderna

Similar to the PFIZER-BIONTECH COVID-19 VACCINE, the nucleoside-modified mRNA in the COVID-19 Vaccine Moderna is formulated in lipid nanoparticles, which enable delivery of the nucleoside-modified mRNA into the host's cells to allow expression of the pre-fusion stabilized Spike glycoprotein (S) of SARS-CoV-2 virus²⁶. The full-length sequence of the SARS-CoV-2 spike protein is modified with 2 proline substitutions within the heptad repeat 1 domain (S-2P) to stabilise the spike protein into a prefusion conformation²⁷. It encodes the spike glycoprotein (S-protein) present on the surface of SARS-CoV-2. The vaccine elicits T and B-cell responses to generate neutralising antibodies to the S antigen, which may contribute to the protection against COVID-19^{28, 29}.

²³ Summary Basis of Decision - Pfizer-BioNTech COVID-19 Vaccine - Health Canada

²⁴ [Product-information/comirnaty-epar-product-information](#)

²⁵ [Product Monograph Pfizer-BioNTech COVID-19 Vaccine](#) dated May 19, 2021

²⁶ <https://www.fda.gov/media/144637/download>

²⁷ https://www.ema.europa.eu/en/documents/product-information/spikevax-previously-covid-19-vaccine-moderna-epar-product-information_en.pdf

²⁸ https://www.ema.europa.eu/en/documents/product-information/spikevax-previously-covid-19-vaccine-moderna-epar-product-information_en.pdf

²⁹ <https://www.fda.gov/media/144637/download>

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Each dose of COVID-19 Vaccine Moderna contains 100 µg of mRNA in a 0.5 mL suspension. Each dose of the COVID-19 Vaccine Moderna also contains the following ingredients: SM-102, polyethylene glycol [PEG] 2000 dimyristoyl glycerol [DMG], cholesterol, and 1,2-distearoyl-sn-glycero-3-phosphocholine [DSPC]) [REDACTED] mg tromethamine, [REDACTED] mg tromethamine hydrochloride, [REDACTED] mg acetic acid, [REDACTED] mg sodium acetate trihydrate, and [REDACTED] mg sucrose.

Both vaccines are formulated as suspensions for intramuscular injection requiring a series of two doses to complete vaccination, administered 21 days apart (PFIZER-BIONTECH COVID-19 VACCINE) and 28 days apart (COVID-19 Vaccine Moderna).

MHPD comments: The COVID-19 Vaccine Moderna contains three times as much mRNA per dose compared to PFIZER-BIONTECH COVID-19 VACCINE. Recent studies have shown that a half-dose³⁰ and a quarter dose³¹ of the COVID-19 Vaccine Moderna seemed to elicit a significant immune response to SARS-COV-2 in participants 18 years and older, which was comparable to the standard dose. On June 02, 2021, ModernaTX, Inc. announced³² that the lower dose version may therefore be given to children, who may not require a full dose. The data from these studies are not yet available to Health Canada for review. As of July 13, 2021, the COVID-19 Vaccine Moderna has only been authorized in the adult population (refer to section 3.1 for further details on the authorized indication).

3.3 Product utilization

3.3.1 PFIZER-BIONTECH COVID-19 VACCINE

Worldwide:

From the latest monthly safety report (MSSR # 6: Covering the month of May 2021; Control #253419)³³, there were approximately 542,013,978 doses of the PFIZER-BIONTECH COVID-19 VACCINE administered from the receipt of the first temporary authorisation (December 01, 2021 through May 31, 2021).

Canada:

From the Canadian COVID-19 Vaccination Coverage Surveillance System (CCVCSS) of the Public Health Agency of Canada (PHAC), it was estimated that 29,570,445 doses of the

³⁰ Chu L, McPhee R, Huang W, et al. A preliminary report of a randomized controlled phase 2 trial of the safety and immunogenicity of mRNA-1273 SARS-CoV-2 vaccine. *Vaccine*. 2021;39(20):2791-2799. doi:10.1016/j.vaccine.2021.02.007

³¹ <https://www.medrxiv.org/content/10.1101/2021.06.30.21259787v1>

³² <https://www.reuters.com/business/healthcare-pharmaceuticals/lonza-add-dutch-production-line-boost-moderna-covid-19-vaccine-2021-06-02/>

³³ Summary Monthly Safety Report (SMSR) 6 covering the Month of May 2021

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PFIZER-BIONTECH COVID-19 VACCINE had been administered in Canada up to July 10, 2021^{34,35}.

3.3.2 COVID-19 Vaccine Moderna

Worldwide:

From the latest monthly safety report (MSSR # 5: Covering period the month of May 2021)³⁶, approximately 155,522,108 doses of the COVID-19 Vaccine Moderna were administered from the receipt of the first temporary authorisation for emergency supply through May 31, 2021. The majority (~80%) was distributed in the United States.

Canada:

From the Canadian COVID-19 Vaccination Coverage Surveillance System (CCVCSS) of the PHAC, it was estimated that 10,304,300 doses of the COVID-19 Vaccine Moderna had been administered in Canada up to July 10, 2021.

MHPD comments: As of July 10, 2021, the data obtained from CCVCSS show that 10,315,093 of the PFIZER-BIONTECH COVID-19 VACCINE doses were administered to recipients under 18 years of age. In comparison, 59,972 COVID-19 Vaccine Moderna doses were administered to recipients under 18 years of age. No further information is provided at this time.

4. Relevant information of COVID-19 disease related to the indication

4.1 COVID-19 Disease

The coronavirus disease 2019 is the infectious disease caused by the recently discovered severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus that emerged in late 2019. In Canada, there have been 1,422,246 confirmed cases of COVID-19 and 26,472 deaths as of July 15, 2021³⁷. Described predominantly as a respiratory disease, the COVID-19 disease is a complex illness ranging from mild to life-threatening. COVID-19 may affect different organs

³⁴ File available on the Health Canada internal Y drive at the following location: \\Ncr-a-irbv1s\irbv1\HC\HPFB\MHPD\MBBNHPB\X_REFERENCE\BBRS CRT\Reference Documents\Doses administered data

³⁵ [COVID-19 vaccination coverage in Canada - Canada.ca](https://www.canada.ca/en/health-canada/services/covid-19/vaccines/covid-19-vaccination-coverage-in-canada.html)

³⁶ Summary Monthly Safety Report (SMSR) 6 covering the Month of May 2021

³⁷ [Coronavirus disease \(COVID-19\): Outbreak update as of July 15, 2021](https://www.canada.ca/en/health-canada/services/covid-19/coronavirus-disease-covid-19-outbreak-update-as-of-july-15-2021.html)

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and tissues of the body including the vascular system^{38, 39}. Symptoms may appear 1 to 14 days after exposure to the virus, and may include fever, chills, cough, shortness of breath, fatigue, muscle or body aches, headache, loss of taste or smell, sore throat, congestion or runny nose, nausea, vomiting, or diarrhea. The majority of patients infected with the SARS-CoV-2 virus recover without significant sequelae. However, 10% to 15% of cases progress to severe disease, and 5% of patients become critically ill. Significant risk factors such as age and underlying medical issues increase the likelihood of developing a severe complication. In around 30% of cases, symptoms may linger or recur over the weeks following the initial recovery, even in patients who had a mild case of the disease⁴⁰.

In general, children, adolescents and young adults have lower incidence and fewer severe COVID-19 outcomes than adults. According to a US study⁴¹, in 0-24 years of age groups, 2.5% were hospitalized, 0.8% required ICU admission, and less than 0.1% died, compared with 16.6%, 8.6%, and 5.0% among adults aged ≥ 25 years, respectively. Rare cases of Multisystem Inflammatory Syndrome in Children (MIS-C) with severe outcomes including fatality have been reported in children; however most children who have MIS-C eventually recover with medical care⁴².

As of July 09, 2021, there were 14 deaths⁴³ recorded in Canada in the 0 to 19 years age group. This corresponds to 0.1% of the COVID-19 fatality cases, compared with 20.2% and 64.4 % among elderly patients aged 70-79 and >80 years, respectively (refer to Figure 1a)⁴⁴. Similar age distribution trends are observed when accounting for COVID-19 hospitalized cases or cases admitted to ICU (Refer to Figures 1b and 1c)⁴⁵.

³⁸ <https://www.cdc.gov/coronavirus/2019-ncov/your-health/about-covid-19/basics-covid-19.html>

³⁹ <https://www.hopkinsmedicine.org/health/conditions-and-diseases/coronavirus/what-does-covid-do-to-your-blood>

⁴⁰ <https://covid-vaccine.canada.ca/info/summary-basis-decision-detailTwo.html?linkID=SBD00519>

⁴¹ Leidman E, Duca LM, Omura JD, Proia K, Stephens JW, Sauber-Schatz EK. COVID-19 Trends Among Persons Aged 0–24 Years — United States, March 1–December 12, 2020. MMWR Morb Mortal Wkly Rep 2021;70:88–94. DOI: <http://dx.doi.org/10.15585/mmwr.mm7003e1>

⁴² <https://www.mayoclinic.org/diseases-conditions/mis-c-in-kids-covid-19/symptoms-causes/syc-20502550>

⁴³ [Canada Health-infobase COVID-19 daily epidemiology update \(as of July 15, 2021\)](#)

⁴⁴ [Canada Health-infobase COVID-19 daily epidemiology update \(as of July 15, 2021\)](#)

⁴⁵ [Canada Health-infobase COVID-19 daily epidemiology update \(as of July 15, 2021\)](#)

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Figure 1a Age and gender ⁴ distribution of COVID-19 cases in Canada as of July 9, 2021, 7 pm EST (n=26,342 ¹)

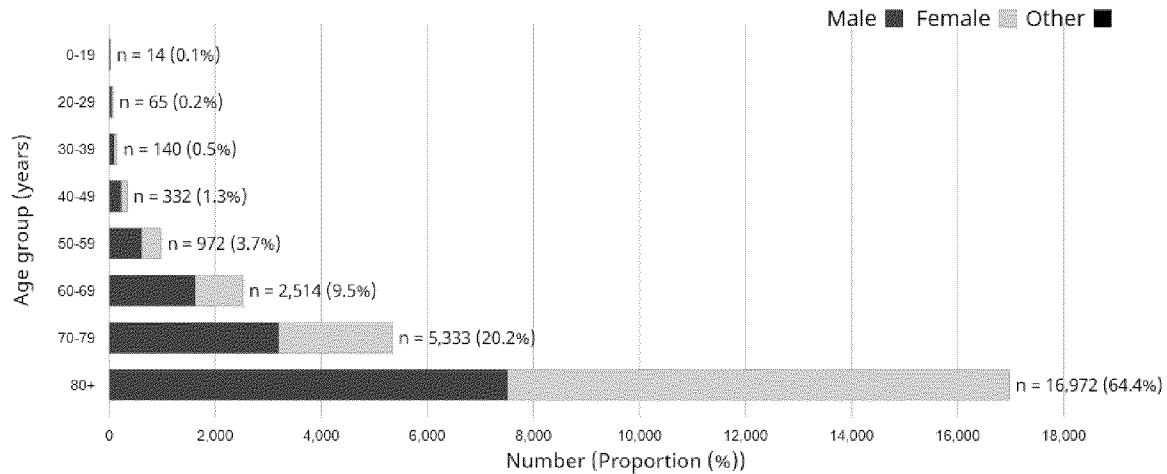
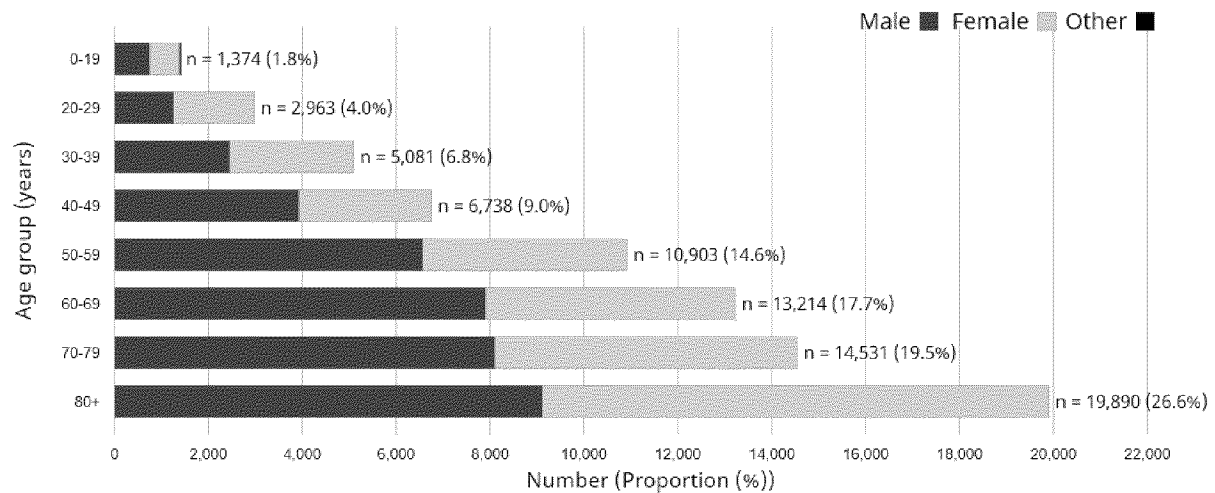
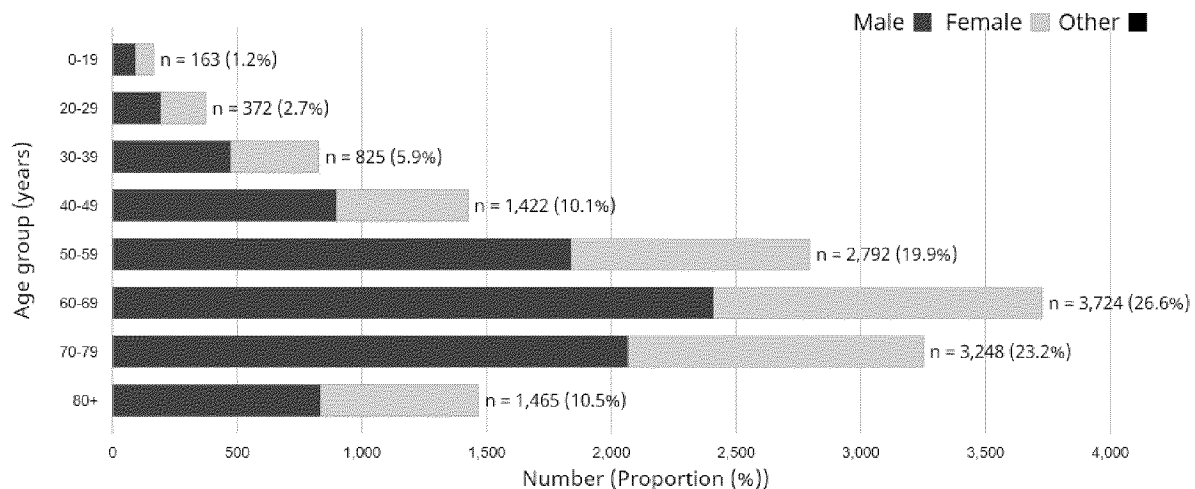


Figure 1b Age and gender ⁴ distribution of COVID-19 cases in Canada as of July 9, 2021, 7 pm EST (n=74,694 ¹)



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Figure 1c Age and gender ⁴ distribution of COVID-19 cases in Canada as of July 9, 2021, 7 pm EST (n=14,011 ¹)



4.2 Preventative vaccine options for the indication

Care for individuals who have COVID-19 has improved with clinical experience, and clinical management of COVID-19.

To date, Health Canada has authorized five COVID-19 vaccines under the IO.

- On 9 December, 2020, the PFIZER-BIONTECH COVID-19 VACCINE was authorized for active immunization to prevent COVID-19 caused by the SARS-CoV-2 virus in individuals 16 years of age and older⁴⁶.
- On 23 December, 2020, the COVID-19 Vaccine Moderna was authorized for active immunization against COVID-19 caused by the SARS-CoV-2 virus in individuals 18 years of age and older. ⁴⁷
- On 26 February 2021, the AstraZeneca COVID-19 Vaccine and COVISHIELD Vaccine were authorized for active immunization of individuals 18 years of age and over for the prevention of coronavirus disease 2019 (COVID-19) ⁴⁸.
- On 5 March 2021, the Janssen COVID-19 Vaccine was authorized for active immunization for the prevention of coronavirus disease-2019 (COVID-19) caused by SARS-CoV-2 virus in individuals 18 years of age and older⁴⁹.

⁴⁶ <https://covid-vaccine.canada.ca/pfizer-biontech-covid-19-vaccine/product-details>

⁴⁷ <https://covid-vaccine.canada.ca/covid-19-vaccine-moderna/product-details>

⁴⁸ <https://www.canada.ca/en/health-canada/services/drugs-health-products/covid19-industry/drugs-vaccines-treatments/vaccines/astrazeneca.html>

⁴⁹ <https://covid-vaccine.canada.ca/janssen-covid-19-vaccine/product-details>

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In the context of the ongoing pandemic, a need for prophylactic vaccine options and/or treatment options remain.

5. Adverse event (s)

5.1 Description of the Adverse Event

Myocarditis is an inflammatory disease of cardiac muscle that is caused by a variety of infectious and noninfectious conditions in adults⁵⁰. Acute pericarditis is an inflammatory disease of the pericardium (the flexible two-layered sac that envelops the heart)⁵¹. The terms myopericarditis, or perimyocarditis, are used for cases of acute pericarditis that also demonstrate myocardial inflammation; myopericarditis is used for cases with prevalent pericarditis and normal ventricular function; perimyocarditis is used for cases with prevalent myocarditis and/or if ventricular function is reduced (new wall motion abnormalities or reduced left ventricular ejection fraction)⁵².

Based on a Finish study, the incidence of myocarditis in children (below 15 years of age) is estimated at 1 to 2 per 100,000 children. The true incidence of myocarditis is unknown and varies by season, age, and geography. Peaks in children and adolescents have been reported in the medical literature; and a recent study reported 2.16 cases per 100,000 US military service members in a 30-day period⁵³.

Sagar et al⁵⁴, note the short-term prognosis of acute myocarditis is usually good but varies widely depending on the etiology. Patients who initially recover might develop recurrent dilated cardiomyopathy sometimes years later.

Clinical manifestations include a broad spectrum of signs including non-specific symptoms such as respiratory distress, and exhaustion. Most patients respond well to standard heart failure

⁵⁰ [Clinical-manifestations-and-diagnosis-of-myocarditis-in-adults](#)

⁵¹ <https://www.merckmanuals.com/home/heart-and-blood-vessel-disorders/pericardial-disease-and-myocarditis/acute-pericarditis>

⁵² [Acute pericarditis: Treatment and prognosis-treatment-and-prognosis](#), UpToDate, Imazio et al, 2021

⁵³ Marshall M, Ferguson ID, Lewis P, et al. Symptomatic acute myocarditis in seven adolescents following Pfizer-BioNTech COVID- 19 vaccination. *Pediatrics*. 2021; doi: 10.1542/peds.2021-052478 ([Case report](#))

⁵⁴ [Myocarditis - The Lancet](#)

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therapy, although in severe cases, mechanical circulatory support or heart transplantation is indicated⁵⁵. In severe cases, myocarditis may lead to cardiogenic shock and sudden death^{56,57,58}.

Myocarditis and/or pericarditis following mRNA vaccination has yet to be fully characterized; however, the spectrum of clinical manifestations appear to be less severe with most patients responding well to treatment and recovering quickly⁵⁹. Myocarditis following mRNA vaccination appears to be age-dependent with cases reported in adolescents and young adults⁶⁰.

5.2. Biological Plausibility

The mechanism of myocarditis and/or pericarditis following mRNA COVID vaccination is not clear. There are numerous proposed mechanisms that include: inflammatory reactions, autoimmune reactions, increased reactogenicity, vaccine dosage and interval, vaccine components and the role of sex hormones in cardiac manifestations.

Beginning of Confidential information

These hypotheses were discussed at the Special expert meeting on vaccine-associated myocarditis and/or pericarditis held on June 25, 2021. The final draft overview of the discussion is included in Appendix 1 and is briefly summarized below:

Host immune response

The production of type-1 interferons and other pro-inflammatory cytokine production may explain a dysregulated immune response, due to an RNA-recognition by pattern recognition receptors. The hypothesis of a possible immune response, that may be triggered by the RNA, is further supported by the quick response to anti-inflammatory treatment not usually seen with “traditional” myocarditis. Furthermore, the COVID-19 Vaccine Moderna which has a higher concentration of mRNA appears to be associated with a higher incidence of myocarditis. In PFIZER-BIONTECH COVID-19 VACCINE Clinical Trials the adolescent population (12-15 years of age) achieved statistically greater immune responses compared to participants 16 to 25 years of age. A reduced dose is currently being studied in younger populations. Previous SARS-CoV-2 infection may be a priming factor that leads to an exaggerated response upon vaccination.

MHPD comments: In the literature, case reports of myocarditis following mRNA COVID-19 vaccination noted that the autoimmune reaction or cross-reactivity between SARS-COV-2

⁵⁵ Blauwet LA, Cooper LT. Myocarditis. *Prog Cardiovasc Dis.* 2010;52(4):274-288. doi:10.1016/j.pcad.2009.11.006

⁵⁶ Blauwet LA, Cooper LT. Myocarditis. *Prog Cardiovasc Dis.* 2010;52(4):274-288. doi:10.1016/j.pcad.2009.11.006

⁵⁷ <https://www.mayoclinic.org/diseases-conditions/cardiogenic-shock/symptoms-causes/syc-20366739>

⁵⁸ Kühl U, Schultheiss HP. Myocarditis in children. *Heart Fail Clin.* 2010;6(4):483-ix. doi:10.1016/j.hfc.2010.05.009

⁵⁹ <https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/myocarditis.html>

⁶⁰ <https://www.cdc.gov/vaccines/covid-19/clinical-considerations/myocarditis.html>

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antigens and myocardial cell proteins may have some role to play on the occurrence of this event^{61,62}.

Differences in the number of cases attributed for each vaccine are discussed under section 6.1.2

Vaccine components

Another hypothesized mechanism of action is the involvement of distinct components of mRNA vaccines (mRNA containing modified nucleosides, lipid nanoparticles etc.) that may play a role in the observed cardiac manifestations including a possible role for the produced spike protein and/or its interaction with cardiac or vascular ACE2 receptors.

MHPD comments: A small study from Harvard University showed evidence of systematic detection of spike and S1 protein production following vaccination of COVID-19 Vaccine Moderna⁶³. The study has detected the involvement of the circulating SARS-CoV-2 protein antigen levels (S1 subunit) as early as one day post-vaccination in plasma samples⁶⁴. S1 subunit protein level peaked on average five days after the first injection⁶⁵. Increased antibody levels correlated with viral protein clearance from plasma. The authors conclude that the evidence of systemic detection of spike and S1 protein production from the mRNA-1273 vaccine is significant; however, the clinical relevance of this finding should be further explored. Yang et al⁶⁶ have previously established that the receptor binding domain of the spike protein serves as the binding interface within the spike glycoprotein with the ACE2 receptor whereas, Nicin et al⁶⁷ found ACE2 to be expressed in cardiomyocytes and pericytes.

Sex differences

⁶¹ Habib MB, Hamamyh T, Elyas A, Altermanini M, Elhassan M. Acute myocarditis following administration of BNT162b2 vaccine. *IDCases*. 2021;25:e01197. Published 2021 Jun 16. doi:10.1016/j.idcr.2021.e01197

⁶² Vojdani A., Kharrazian D. Potential antigenic cross-reactivity between SARS-CoV-2 and human tissue with a possible link to an increase in autoimmune diseases. *Clin Immunol*. 2020;217 doi: 10.1016/j.clim.2020.108480

⁶³ Ogata AF, Cheng CA, Desjardins M, et al. Circulating SARS-CoV-2 Vaccine Antigen Detected in the Plasma of mRNA-1273 Vaccine Recipients [published online ahead of print, 2021 May 20]. *Clin Infect Dis*. 2021;ciab465. doi:10.1093/cid/ciab465

⁶⁴ Ogata AF, Cheng CA, Desjardins M, et al. Circulating SARS-CoV-2 Vaccine Antigen Detected in the Plasma of mRNA-1273 Vaccine Recipients [published online ahead of print, 2021 May 20]. *Clin Infect Dis*. 2021;ciab465. doi:10.1093/cid/ciab465

⁶⁵ Ogata AF, Cheng CA, Desjardins M, et al. Circulating SARS-CoV-2 Vaccine Antigen Detected in the Plasma of mRNA-1273 Vaccine Recipients [published online ahead of print, 2021 May 20]. *Clin Infect Dis*. 2021;ciab465. doi:10.1093/cid/ciab465

⁶⁶ Yang, J., Petitjean, S.J.L., Koehler, M. *et al*. Molecular interaction and inhibition of SARS-CoV-2 binding to the ACE2 receptor. *Nat Commun* **11**, 4541 (2020). <https://doi.org/10.1038/s41467-020-18319-6>

⁶⁷ Nicin L, Abplanalp WT, Mellentin H, et al. Cell type-specific expression of the putative SARS-CoV-2 receptor ACE2 in human hearts. *Eur Heart J*. 2020 May 14; 41(19):1804-1806.

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The prevalence of myocarditis in young males may be attributed to signal potentiation by male hormones whereas female hormones have been previously shown to be cardio-protective.

End of Confidential information

MHPD comments: Overall, the potential mechanism of action leading to myocarditis and/or pericarditis following mRNA vaccination remains unclear. The EMA requested further explanation from BioNTech Manufacturing GmbH/ Pfizer Manufacturing Belgium NV regarding the potential mechanisms leading to these adverse events following immunization. These requests are discussed below.

6. Issue Analysis

6.1 Regulatory assessments and/or Actions in Canada and internationally including vaccines committee recommendations

6.1.1 Current Canadian and International Labelling

6.1.1.1 Health Canada

On June 30, 2021, the CPMs for COVID-19 Vaccine Moderna and PFIZER-BIONTECH COVID-19 VACCINE were revised to include the risk of myocarditis and pericarditis.

MHPD comment: Following the ACIP on June 23-25, 2021, Health Canada was informed via confidential agreement that the USPI for PFIZER-BIONTECH COVID-19 VACCINE would be updated to reflect the risk of myocarditis and pericarditis following vaccination with this vaccine. On June 25, a courtesy copy of the draft USPI was shared by the FDA with Health Canada (refer to Appendix 2). Similarly, on the same day, the MHRA updated their labelling for the COVID-19 Vaccine Moderna on myocarditis and pericarditis.

On the same date, the Biologic and Radiopharmaceutical Drug Directorate (BRDD) in collaboration with the MHPD issued advisement letters to both MAHs to include the risk of myocarditis and/or pericarditis in the product monographs under the Warnings and Precautions section, Post-market adverse events section and the patient information section. (Pfizer Canada ULC, [HC6-024-e243022 \(1.0\) Reg Info - Health Product](#) (DSTS control # 254161) and ModernaTX, Inc. [HC6-024-e244946 \(1.0\) Reg Info - Health Product](#) (DSTS control #254172))

The CPMs for the PFIZER-BIONTECH COVID-19 VACCINE⁶⁸ and the COVID-19 vaccine Moderna⁶⁹ were updated on June 30, 2021. Refer to section 6.1.5 for detailed product monograph

⁶⁸ https://pdf.hres.ca/dpd_pm/00061958.PDF

⁶⁹ https://pdf.hres.ca/dpd_pm/00061956.PDF

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warnings and precautions statements, post-market adverse reactions and patient medication information regarding myocarditis and pericarditis.

6.1.1.2 European Medicines Agency (EMA)

The PRAC adopted a recommendation to initiate a signal assessment on this issue in May 2021. Recommendations stemming from this review were shared during the July PRAC meeting and mRNA vaccine labelling updates were published on July 09, 2021⁷⁰. The Summary of Product Characteristics (SmPCs) were updated on July 22, and July 26, 2021 for the PFIZER-BIONTECH COVID-19 VACCINE⁷¹ and the COVID-19 Vaccine Moderna⁷², respectively.

6.1.1.3. Food and Drugs Administration

On June 23, 2021, the FDA confirmed their intention during the ACIP June meeting to add myocarditis and pericarditis to the mRNA COVID Vaccines fact sheets. The FDA confirmed that a warning statement would be added in the fact sheet for PFIZER-BIONTECH COVID-19 VACCINE about the increased risks of myocarditis and pericarditis, particularly following the second dose. Typically, onset of symptoms has been within a few days following receipt of the mRNA COVID-19 Vaccine. Available data from short-term follow-up suggest that most individuals have had resolution of symptoms, but information is not yet available about potential long-term sequelae. The decision to administer the PFIZER-BIONTECH COVID-19 VACCINE to an individual with a history of myocarditis or pericarditis should be taken into account in the individual's clinical circumstances. The CDC has published information regarding clinical considerations on myocarditis and pericarditis following vaccination with the PFIZER-BIONTECH COVID-19 VACCINE (<https://www.cdc.gov/vaccines/covid-19/clinical-considerations/myocarditis.html>).

The FDA updated the mRNA COVID vaccines label on June 25, 2021.

6.1.1.4 Medicines and Healthcare products Regulatory Agency (MHRA)

On June 25, 2021, the MHRA updated their "Information for Healthcare Professionals and patient information on mRNA Covid-19 vaccines to include the risk of myocarditis and pericarditis.

⁷⁰ https://www.ema.europa.eu/en/documents/product-information/comirnaty-epar-product-information_en.pdf

⁷¹ Comirnaty | European Medicines Agency (europa.eu)

⁷² "Spikevax, INN-COVID-19 mRNA Vaccine (nucleoside modified)" (europa.eu)

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Canada (HC)⁷⁴	United States (FDA)⁷⁵	UK (MHRA)⁷⁶	EMA (Europe)⁷⁷
Warnings and Precautions/Cardiovascular/ Myocarditis and Pericarditis Very rare cases of myocarditis and/or pericarditis following vaccination with Pfizer-BioNTech COVID-19 Vaccine have been reported during post-authorization use. These cases occurred more commonly after the second dose and in adolescents and young adults. Typically, the onset of symptoms has been within a few days following receipt of the Pfizer-BioNTech COVID-19 Vaccine. Available short-term follow-up data suggest that the symptoms resolve in most individuals, but information on long-term sequelae is lacking. The decision to administer the Pfizer-BioNTech COVID-19 Vaccine to an individual with a history of myocarditis or pericarditis should take into account the individual's clinical circumstances. Healthcare professionals are advised to consider the possibility of myocarditis and/or pericarditis in their differential diagnosis if individuals present with chest	Warnings Myocarditis and Pericarditis Reports of adverse events following use of the Pfizer-BioNTech COVID-19 Vaccine under EUA suggest increased risks of myocarditis and pericarditis, particularly following the second dose. Typically, onset of symptoms has been within a few days following receipt of the Pfizer-BioNTech COVID-19 Vaccine. Available data from short-term follow-up suggest that most individuals have had resolution of symptoms, but information is not yet available about potential long-term sequelae. The decision to administer the Pfizer-BioNTech COVID-19 Vaccine to an individual with a history of myocarditis or pericarditis should take into account the individual's clinical circumstances. The CDC has published clinical considerations relevant to myocarditis and pericarditis associated with administration of the	4.4 Special warnings and precautions for use Myocarditis and pericarditis There have been very rare reports of myocarditis and pericarditis occurring after vaccination with COVID-19 mRNA Vaccine BNT162b2 often in younger men and shortly after the second dose of the vaccine. These are typically mild cases and individuals tend to recover within a short time following standard treatment and rest. Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccinated individuals should also seek immediate medical attention should they experience new onset of chest pain, shortness of breath, palpitations or arrhythmias.	4.4 Special warnings and precautions for use Myocarditis and pericarditis Very rare cases of myocarditis and pericarditis have been observed following vaccination with Comirnaty. These cases have primarily occurred within 14 days following vaccination, more often after the second vaccination, and more often in younger men. Available data suggest that the course of myocarditis and pericarditis following vaccination is not different from myocarditis or pericarditis in general. Healthcare professionals should be alert to the signs and

⁷³ PFIZER-BIONTECH COVID-19 VACCINE used as an example, similar labeling for COVID-19 Vaccine Moderna

⁷⁴ https://pdf.hres.ca/dpd_pm/00061958.PDF

⁷⁵ <https://www.fda.gov/media/144413/download>

⁷⁶ <https://www.gov.uk/government/publications/regulatory-approval-of-pfizer-biontech-vaccine-for-covid-19/information-for-healthcare-professionals-on-pfizerbiontech-covid-19-vaccine>

⁷⁷ [Comirnaty, INN-COVID-19 mRNA Vaccine \(nucleoside-modified\) \(europa.eu\)](https://www.comirnaty.eu/)

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Canada (HC)⁷⁴	United States (FDA)⁷⁵	UK (MHRA)⁷⁶	EMA (Europe)⁷⁷
pain, shortness of breath, palpitations or other signs and symptoms of myocarditis and/or pericarditis following immunization with a COVID-19 vaccine. This could allow for early diagnosis and treatment. Cardiology consultation for management and follow up should be considered.	Pfizer-BioNTech COVID-19 Vaccine (https://www.cdc.gov/vaccines/covid-19/clinicalconsiderations/myocarditis.html).		symptoms of myocarditis and pericarditis. Vaccinees should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination. Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition.
Post-Market Adverse Reactions Cardiac disorders: myocarditis and/or pericarditis	Adverse reactions Myocarditis and pericarditis have been reported following administration of the Pfizer-BioNTech COVID-19 Vaccine outside of clinical trials.	4.8 Undesirable effects Cardiac disorders Not known: Myocarditis, pericarditis. (Adverse reaction determined post authorisation.)	4.8 Undesirable effects Myocarditis; Pericarditis frequency Not known (cannot be estimated from the available data)
PATIENT MEDICATION INFORMATION To help avoid side effects and ensure proper use, talk to your healthcare professional before you receive Pfizer-BioNTech COVID-19 Vaccine. Talk about any health conditions or problems you may have,			Package leaflet: Information for the user Very rare cases of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside

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Canada (HC)⁷⁴	United States (FDA)⁷⁵	UK (MHRA)⁷⁶	EMA (Europe)⁷⁷
including if you: • have previously had episodes of myocarditis and/or pericarditis			the heart) have been reported after vaccination with Comirnaty. The cases have primarily occurred within two weeks following vaccination, more often after the second vaccination, and more often occurred in younger men. Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur.

6.1.2 Analysis of Adverse Events in Canada and Internationally**6.1.2.1 Cases reported during the clinical development**

At the time of this review, there were no reported cases of myocarditis and/or pericarditis occurring after PFIZER-BIONTECH COVID-19 VACCINE and COVID-19 Vaccine Moderna administration in the clinical trials at time of authorization^{78,79}.

Cardiac events were reported during the PFIZER-BIONTECH COVID-19 VACCINE trial. One related serious adverse event was reported among the BNT162b2 recipients (paroxysmal ventricular arrhythmia). Two BNT162b2 recipients died (one from arteriosclerosis, one from

⁷⁸ Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, Diemert D, Spector SA, Rouphael N, Creech CB, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. *N Engl J Med*. 2021;384:403-416.

⁷⁹ 2. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, Perez JL, Pérez Marc G, Moreira ED, Zerbini C, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *N Engl J Med*. 2020 Dec 31;383:2603-2615

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cardiac arrest), as did four placebo recipients (two from unknown causes, one from hemorrhagic stroke, and one from myocardial infarction). No deaths were considered related to the vaccine⁸⁰.

6.1.2.2 Cases reported during post-market reported in the Monthly Safety Reports

PFIZER-BIONTECH COVID-19 VACCINE

Discussion retrieved from the review of the Monthly Safety Report 5, DSTS# 251813 (Verbatim excerpts⁸¹)

The potential risk of myocarditis with the Pfizer BioNtech vaccine was raised on 15 February 2021, triggered by ongoing discussions with Israel Ministry of Health. The MAH conducted a cumulative review of myocarditis/pericarditis at the request of the MHRA on April 19, 2021. As noted by the MAH the reason for evaluation was “to determine if myocarditis or pericarditis is a risk”.

On 15 May 2021, Pfizer provided to Health Canada a cumulative review of Myocarditis and Pericarditis in the MSR 5. The cumulative review included cases from the unblinded clinical study data and from Pfizer’s safety database. The database was searched for spontaneous adverse events reports for Pfizer/BNT COVID-19 vaccine using the PTs “Myocarditis”, “Pericarditis”, and “Pericardial effusion” up to 17 April 2021. Results are summarized below:

Unblinded clinical study data (C459001) (up to 13 March 2021) searched for cases of myocarditis and pericarditis:

From the clinical trial C459001 one myocarditis case was reported in the placebo group and one pericarditis case was reported in the BNT162b2 group. Both cases were received during the blinded placebo-controlled follow-up period. The case reported in the BNT162b2, a 66 year old white male who had pericarditis 29 days after dose 2 of vaccine, was ongoing at the time of the data cut-off. The investigator assessed the case as not related to study intervention

Post-authorization data (up to April 17, 2021)

Upon search of the database the MAH retrieved 278 cases including 31 reports coded with the PT pericardial effusion (without Pericarditis or Myocarditis). Of these, 29 were excluded from further analysis. These cases described a pericardial effusion that may be attributed to other diseases or did not contain enough clinical data. Of the remaining cases; 104 cases were coded with the PT Pericarditis, 127 cases were coded for myocarditis and 16 cases for myocarditis and pericarditis. Upon further analysis, the MAH excluded 30 reports because they provided

⁸⁰ Polack F.P., Thomas S.J., Kitchin N., Absalon J., Gurtman A., Lockhart S. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med. 2020;383:2603–2615. doi: 10.1056/nejmoa2034577

⁸¹ Approved on June 04, 2021

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alternative explanations for potential pericarditis or myocarditis including COVID-19, history of autoimmune condition, renal failure and histories of tuberculosis.

- *The remaining 216 reports described 92 cases of pericarditis including one fatality and 124 cases of myocarditis (108 cases reported under the PT Myocarditis and 16 cases under the PT Pericarditis and Myocarditis) including 3 fatalities (and summarized below and in Table 1 by reviewer).*

Pericarditis cases (92 cases)

- *50% cases (46/92) occurred following Dose 1 35% (32/92) cases occurred following Dose 2.*
- *1 case reported Pericarditis following D1 and D2. One case from Israel described pericarditis occurring after dose 1 (reported AE: permyocarditis) and dose 2 (reported AE: pericarditis). Medical history included hypertension and dyslipidemia. A smoker and had tooth extraction (received antibiotics). Outcome is unknown*
- *57% cases (52/92) occurred between 0 (same day) to 7 days following vaccination (Range 0-41 days, median 2-7 days)*
- *Median Age reported was 49 years (Range 17-88)*
- *53% (49/92) cases are in male patients , 46% patients are in female patients*
- *40 % (37/92) patients recovered, 13% (12/92) recovered with sequelae, 22% (20/92) not recovered*
- *1 death was reported*
- *Includes 1 Canadian case (no further information provided)*
- *24 cases reported having ECGs, 27 reported having echocardiograms and 15 reported having both*
- *15 cases described pericardial effusions or pericardiocentesis*
- *14/92 cases reported from Israel*
 - *5 cases occurred after dose 1 and 9 after dose 2*
 - *Time to onset: 1 to 7 days*
 - *Medical history: pericarditis (1 case), prostate (1 case) and bladder cancer (1 case), aortic valve replacement (1 case)*

Myocarditis cases (108 cases)

- *17% cases (18/108) occurred following Dose 1, 70% (32/92) cases occurred following Dose 2*
- *The vast majority of cases (70%) occurred between 0 (same day) to 7 days following vaccination (Range 0-41 days, median 2-7 days)*
- *Median Age reported was 30.8 years (Range 16-81)*

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- The vast majority of cases (76%) are in male patients , 23% patients are in female patients
- 13% (14/108) patients recovered, 11% (12/92) recovered with sequelae, 17% (18/108) not recovered, the outcome was not reported in 62 cases.
- 2 deaths were reported
- Includes 1 Canadian case (no further information provided)
- 3 cases with history of myocarditis or myopericarditis prior to vaccination and 8 had a history of COVID-19.
- 47 cases had varying combinations of inflammatory biomarkers
- None were diagnosed by endomyocardial biopsy for histology (considered by MAH to be gold-standard for diagnosis)
- 54 cases were reported from Israel
 - 7/54 cases occurred after dose 1 and 44/54 occurred after dose 2
 - Time to onset: 1 to 5 days
 - Only two cases with medical history information: myocarditis (1) and perimyocarditis (1) No lab or imaging information is known by the MAH 52 cases with unknown outcome

Myocarditis+Pericarditis cases (16 cases)

- 50% cases (8/16) occurred following Dose 1, 25% (4/16) cases occurred following Dose 2 (the remaining unknown)
- The vast majority of cases (69%) occurred between 0 (same day) to 7 days following vaccination (Range 0-21 days, median 2-7 days)
- Median Age reported was 25 years (Range 17-81)
- The vast majority of cases (75%) are in male patients with 13% in female patients
- 63% (10/16) patients recovered/recovering, 11% (12/92), 6% (1/16) not recovered, the outcome was not reported in 4 cases.
- 1 death was reported

Evaluator comments: The MAH retrieved 278 spontaneous reports based on the initial search criteria including the following PT terms: “Myocarditis”, “Pericarditis” and “Pleural Effusion”.

The MAH reviewed these 278 reports and eliminated the ones that:

- did not contain enough clinical detail;
- described pericardial effusion without pericarditis or myocarditis;
- described pericardial effusion attributed to other diseases

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-did not contain information describing pericarditis or myocarditis
 -had alternative explanations for pericarditis or myocarditis (including current COVID-19, history of autoimmune condition, renal failure, histories of tuberculosis.

The MAH analyzed the remaining 216 cases:

From the analysis of the 216 cases, a pattern emerges from the time to vaccination to the emergence of myocarditis and/or pericarditis. The majority of cases were reported from the same day of vaccination up to 7 days following vaccination. The vast majority (95%, 11/216)) of the cases were reported within 3 weeks of vaccination. However, some cases were reported up to 41 days following vaccination.

Out of the 216 patients, 67 patients had either recovered, had recovered with sequelae or were recovering, 39 had not recovered and 3 deaths were reported.

Of the initial 216 cases, 92 cases described events of pericarditis including one fatality in a 72 year old woman. 42/92 (46 %) were reported in female patients and 49/92 (53%) were reported in male patients.. Half of the cases of pericarditis occurred following the first dose.

Of the initial 216 cases, 108 cases described events of myocarditis and 16 cases reported events of both Pericarditis and Myocarditis for a total of 124 cases reporting an event of myocarditis including 3 fatalities (a 19 year old male patient, a 49 year old male patient and an 81 year old woman). The vast majority of the myocarditis cases were reported in male patients. Furthermore, the majority of the myocarditis cases were reported following the second dose.

The MAH further assessed the 108 cases of myocarditis. The MAH applied a recognized case definition proposed by Bonaca et al to define a myocarditis diagnosis based on three levels of certainty described in this review. By applying the Bonaca approach to diagnosis excluding all other diagnosis/explanations such as coronary syndrome, the MAH retrieved 8 definite cases of myocarditis, 10 probable cases and 21 possible cases for a total of 39 cases meeting a certain level of certainty in diagnosis based on the applied criteria. Out of the 39 cases, 20 were reported in male patients and 19 in female patients all occurring within a common interval of 1 to 7 days following vaccination. (detailed below)

Table 1 Summary of Pericarditis and Myocarditis Cases from SMSR5 (compiled by reviewer)

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Post-authorization data from SMSR 5	92* reports of pericarditis	108 reports Myocarditis	16 reports Pericarditis and Myocarditis
		124 cases	
Time to onset (when specified)	Same day as vaccination (6), 1 day after (15) 2-7 days (31) 8 to 21 days (23) 22 to 41 (10)	Same day as vaccination (14), 1 day after (16) 2-7 days (40) 8 to 21 days (7) 22 to 41 (1)	1 day after (2) 2-7 days (9) 8 to 21 days (2)
Occurrence (when specified)	46 cases after D1 32 cases after D2 13 cases unspecified 1 case after D1 and D2	18 cases after D1 75 cases after D2 15 cases unspecified	8 cases after D1 4 case after D2 4 cases unspecified
Age	17-88 years (mean 51.5, median 49) <u>14/92 cases from Israel</u> 17-70 years (mean 37, median 32)	16-81 years (mean 30.8, median 27) <u>54/108 cases from Israel</u> 16-56 years (mean 25.3, median 22.5)	17-81 years (mean 31.2, median 25) 12/16 cases from Israel 17-48 years (mean 27.4, median 25)
Sex	49 Males, 42 females 14/92 cases from Israel (12 males, 2 females)	82 males, 25 females 54/108 cases from Israel (50 males, 4 females)	12 males, 4 females 12/16 cases from Israel (11 males, 1 female)
Underlying medical condition	14/92 history of pericarditis prior to vaccination and 7 had a history of COVID-19	3/108 history of myocarditis/myopericarditis 8/108 history of COVID-19	
Outcome (when specified)	Recovered/Recovered with sequelae (12) Recovering (37) Not recovered (20)	Recovered/Recovered with sequelae (12) Recovering (14) Not recovered (18) Unknown (62)	Recovered (4) Recovering (6) Not recovered (1) Unknown (4)
Death	1 (72 yo, woman TTO: 3 days after dose 1, Death day 8, UK)	2 (47 yo, male, TTO: unk, after dose 1, Israel) (19 yo, Death day 5 following second, Israel)	1 (81 yo, woman, TTO: 3 days, Death day 5, Austria)
Canadian case	1	1	

*1*104 Pericarditis+ 2 Pericardial effusion= 106.13 cases further excluded (alternative explanations/no information describing event) =92 cases presented in the PSUR*

The MAH assessed the cases of myocarditis using the following category (Bonaca et al):

Definite myocarditis:

- 1. Tissue pathology OR*
- 2. Diagnostic cardiac magnetic resonance imaging (CMR) + clinical syndrome + elevated biomarker or ECG evidence, OR*

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3. *New wall motion abnormality on echocardiogram + Clinical syndrome + elevated biomarker + ECG evidence + Negative angiography*

Probable myocarditis:

1. *Diagnostic CMR without any of the following: clinical syndrome, elevated biomarker or ECG evidence OR*
2. *Suggestive CMR with at least one of the following: clinical syndrome, elevated biomarker or ECG evidence OR*
3. *New wall motion abnormality on echocardiogram and clinical syndrome and 1 of the following: elevated biomarker or ECG evidence OR*
4. *Possible myocarditis with PET scan evidence and no alternative diagnosis*

Possible myocarditis:

1. *Suggestive CMR without any of the following: clinical syndrome, elevated biomarker or ECG evidence OR*
2. *New wall motion abnormality on echocardiogram and one of the following: clinical syndrome, ECG evidence OR*
3. *Elevated biomarker and one of the following: clinical syndrome, ECG evidence*

Of the 108 cases, the MAH found:

1. *8 definite cases of myocarditis: 5 males and 3 female; aged range 19 to 81; 6 cases occurred after dose 2 with the time to onset 1 to 7 days*
2. *10 probable cases: 4 males and 6 females, aged range 12 to 81, 5 cases occurred in dose 1 with common onset interval of 1 to 7 days)*
3. *21 possible cases: 11 males, 9 females and 2 unspecified; aged range 16 to 56; 14 cases occurred after dose 2 with common interval of 1 to 7 days.*

MAH's assessment:

- *The MAH concludes that a causal association between myocarditis and pericarditis with the vaccine is not supported at this time.*
- *Pfizer closed the signal and will continue to monitor myocarditis and pericarditis through spontaneous reporting or via any future publications.*

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Late Breaking information from Israel (as of June 01, 2021)

- There were 275 cases of myocarditis have been reported between December 2020 and May 2021.
- Of these, 148 myocarditis cases occurred around the time of vaccination
- 27 cases reported after dose 1 out of a total of 5,401,150 vaccinated individuals (of which 11 are vaccinated individuals with pre-existing conditions)
- 121 cases reported after dose 2 out of a total of 5,049,424 vaccinated individuals (of which 60 are vaccinated individuals with pre-existing conditions).
- Conclusion: A possible link between the second vaccine dose and the onset of myocarditis among young men aged 16 to 30. Stronger link is observed among the younger age group, 16 to 19, compared to other age groups. In most cases myocarditis took the form of mild illness that passed within a few days.

Canadian cases as of May 21, 2021

23 cases of myocarditis are currently being assessed for causality from the Canadian databases (ongoing).

Canadian and International Governmental Agencies' Actions (ongoing)

No regulatory actions have been taken to date regarding myocarditis

Ongoing information has been communicated through international working groups that include international regulator partners such as the EMA, FDA, MHRA, etc.

Communications regarding the nature of this event and ongoing monitoring have been issued from the CDC^{82, 83} and EMA⁸⁴ and the WHO⁸⁵.

The pattern that has been observed internationally is that these events:

Occur more in males adolescents and young adults age 16 years or older

⁸² [CDC clinical-considerations/myocarditis](https://www.cdc.gov/media/releases/2021/s0511-covid19-myocarditis.html)

⁸³ [Myocarditis and Pericarditis Following mRNA COVID-19 Vaccination | CDC](https://www.cdc.gov/media/releases/2021/s0511-covid19-myocarditis.html)

⁸⁴ [EMA-covid-19-vaccine-safety-update as of May 11, 2021](https://www.ema.europa.eu/en/press/news/2021-05-11-ema-covid-19-vaccine-safety-update)

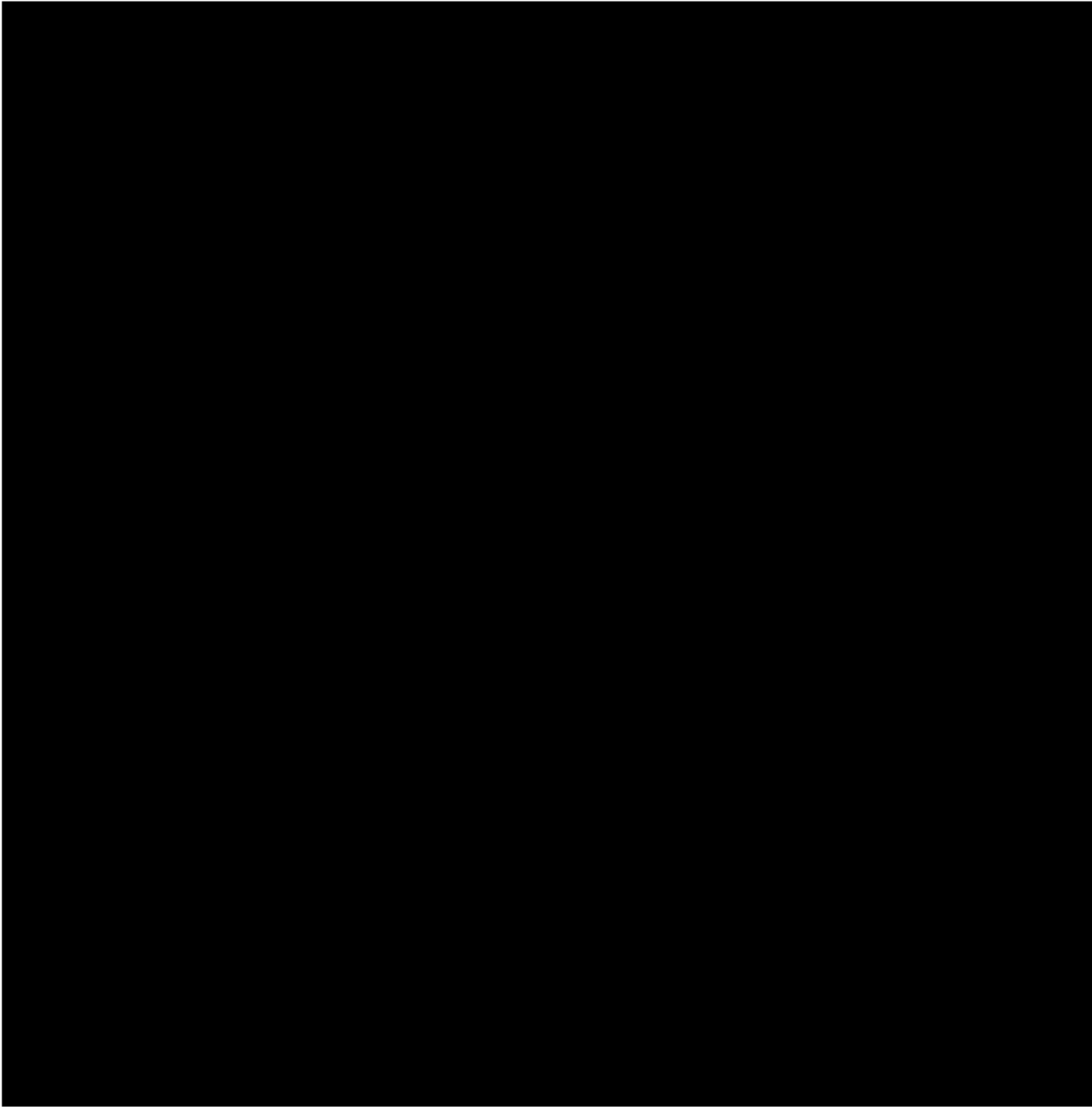
⁸⁵ <https://www.who.int/news/item/26-05-2021-gacvs-myocarditis-reported-with-covid-19-mrna-vaccines>

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Occur more often after getting the second dose of one of these two COVID-19 vaccines than after the first dose

Occur typically within several days after COVID-19 vaccination



⁸⁶ Bonaca MP et al. Myocarditis in the setting of cancer therapeutics: proposed case definitions for emerging clinical syndromes in cardio-oncology. Circulation. 2019; 140:80-91

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Discussion retrieved from the review of the Monthly Safety Report 6, DSTS# 253419 (Verbatim excerpts)

In the Monthly Safety report #6 (DSTS# 253419)⁹⁰, the MAH retrieved 495 reports of myocarditis and pericarditis (up to May 25, 2021). Of the 495, there were 260 cases of myocarditis (all assessed as serious), 73 met a certainty in diagnosis of myocarditis when

⁸⁷ <https://www.gov.il/en/departments/news/01062021-03>

⁸⁸ <https://www.sciencemag.org/news/2021/06/israel-reports-link-between-rare-cases-heart-inflammation-and-covid-19-vaccination>

⁸⁹ [Surveillance of Myocarditis \(Inflammation of the Heart Muscle\) Cases Between December 2020 and May 2021 \(Including\) | Ministry of Health \(www.gov.il\)](#)

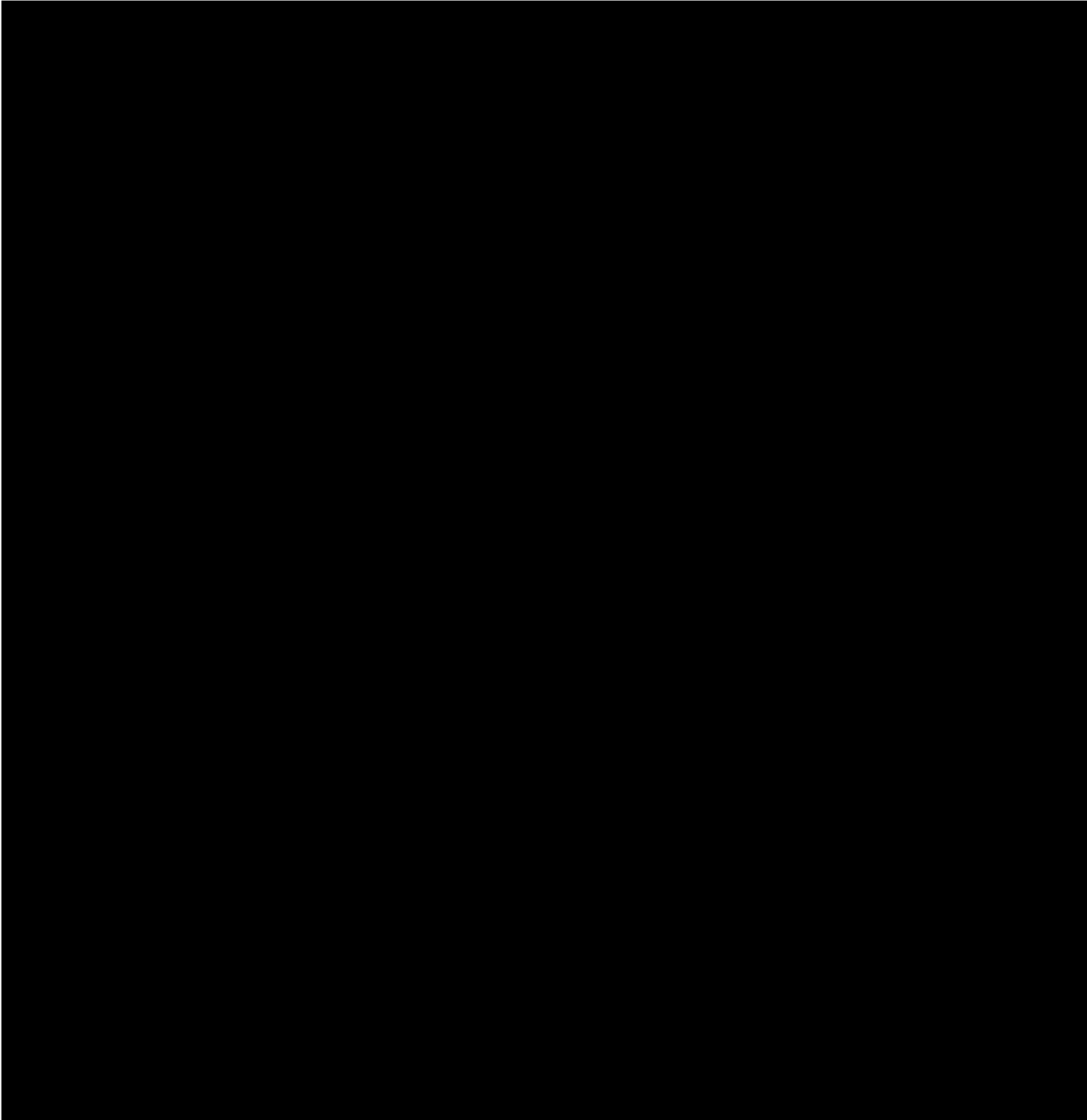
⁹⁰ [HC6-024-e243022 \(253419 - Response to MHPD Request dated 2021-06-07\) - Summary Monthly Safety Report 6 30-APR-2021 through 31-May-2021](#)

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assessed based on the Brighton’s Collaboration (BC) diagnostic certainty criteria. Eighteen (18) cases were classified as BC Level 1 (confirmed), 24 cases as BC level 2 (probable), 31 cases as BC level 3 (possible).

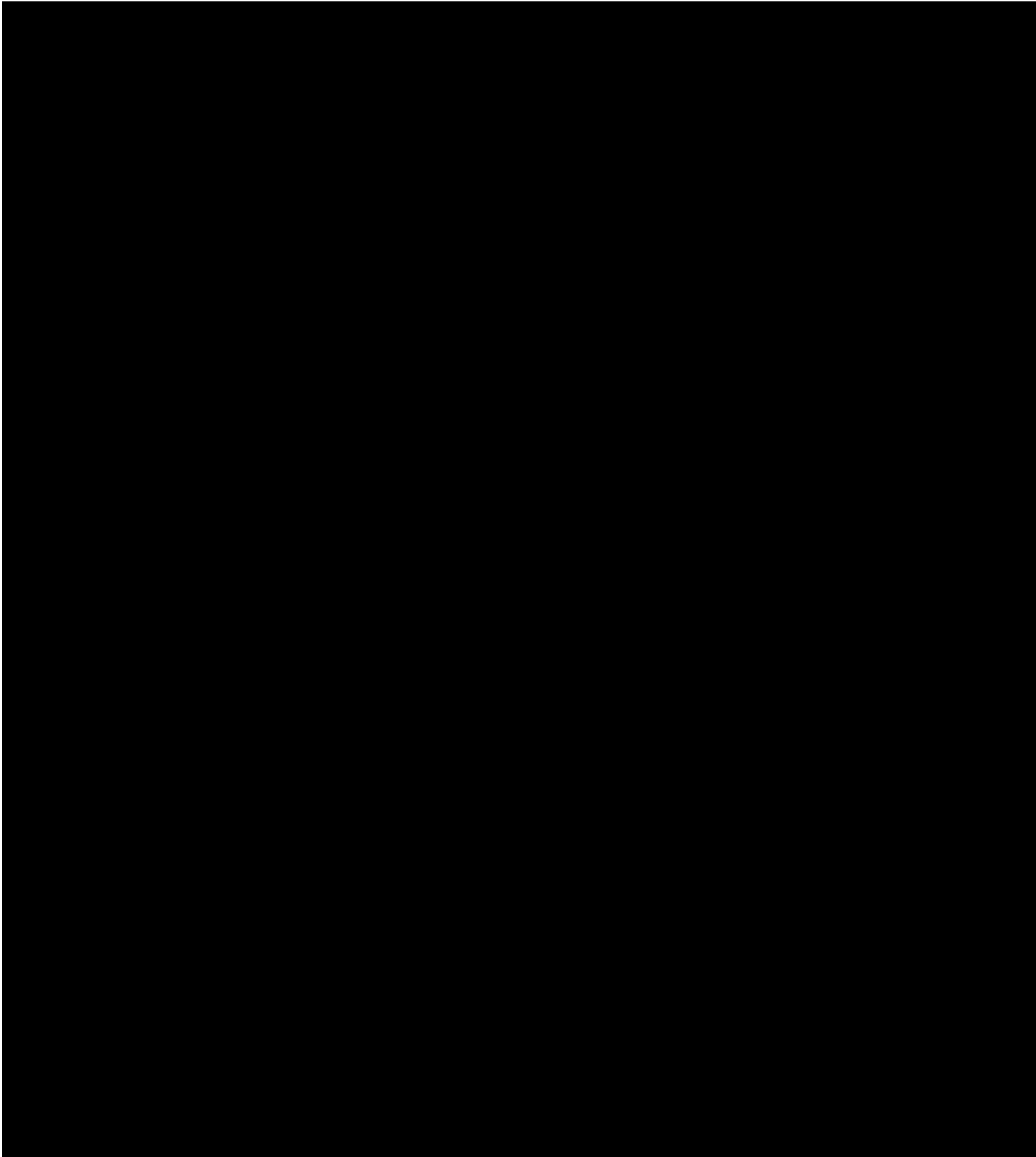
The majority of the confirmed, probable and possible myocarditis case reports were in younger age groups below 39 years of age (48/73; 66%). There were more males than females. 2 cases assessed as possible myocarditis were from Canada.



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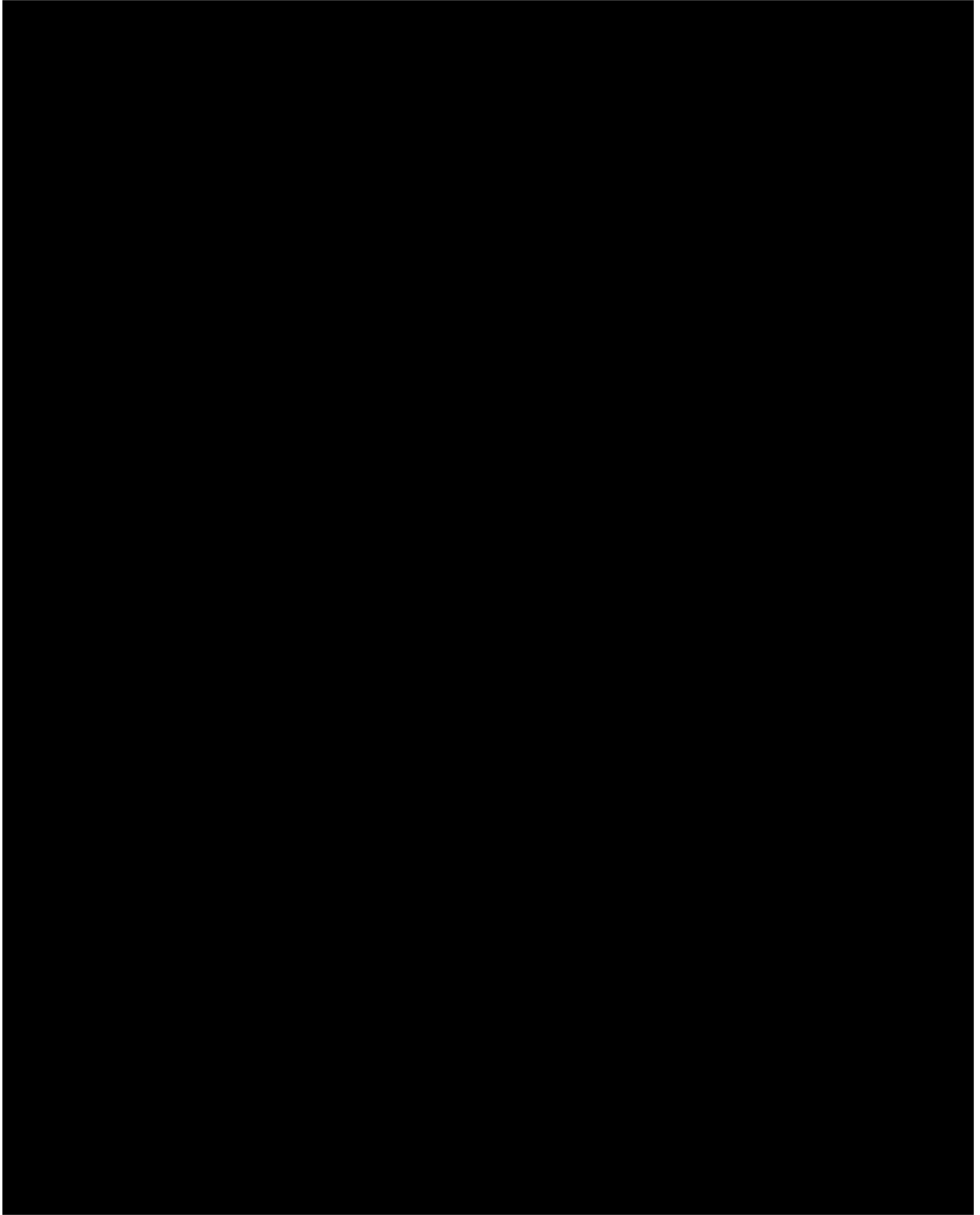
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COVID-19 Vaccine Moderna

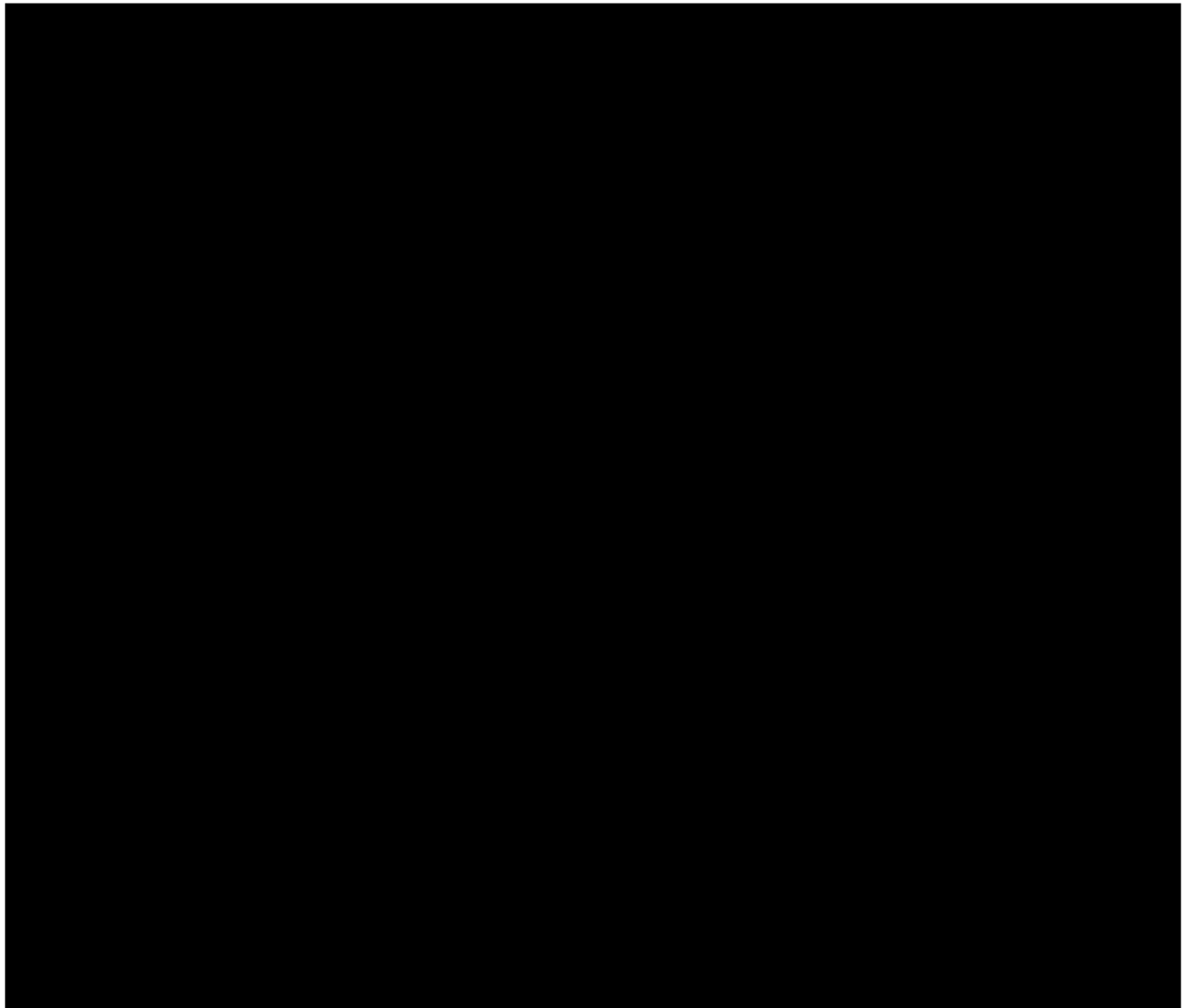


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6.1.2.3 Canadian post-market cases from the Canada vigilance database and CAEFISS database

As of data up to and including July 09, 2021, there were 111 cases of myocarditis/pericarditis following the PFIZER-BIONTECH COVID-19 VACCINE (rate per 100,000 doses administered: 0.40). Sixty-seven cases were seen following the first dose and 26 cases following the second dose. Forty cases were reported following the COVID-19 Vaccine Moderna (rate per 100,000 doses administered: 0.45), 13 cases were reported following the first dose of the vaccine and 20 cases following the second dose. Based on an observed vs expected analysis by vaccine type, age groups and sex, using a time at risk of 7 and 21 days, a signal (increase in the observed vs expected cases) was detected in male patients between 12 to 17 years of age following second dose of the PFIZER-BIONTECH COVID-19 VACCINE. For COVID-19 Vaccine Moderna, a signal was detected in male patients in the 18 to 29 age groups following second dose. When

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combining the data of both mRNA vaccines, a signal is detected in males aged 12 to 17 years and aged 18 to 29 years following the second dose of the vaccines.

MHPD comments: Reports from the PHAC database up to May 2021 showed a statistical signal in all 5 statistical signal detection methods used to assess safety data for myocarditis following immunization with the PFIZER-BIONTECH COVID-19 VACCINE. The statistical signal was also detected in June. Upon labelling the myocarditis/pericarditis events in Canada, there were 90 cases⁹¹ that had been reported to the Canada. Sixty-four cases were reported following Pfizer vaccination and 25 following vaccination with other COVID-19 vaccines. The majority of myocarditis cases following the Pfizer vaccination were after the first dose, and the rate per 100,000 doses administered is the same after first and second dose. Just over half the cases are in females with a median age of 42 years.

Beginning of Confidential Information

As per the June report shared by PHAC⁹²:

The observed cases of myocarditis/pericarditis cases following vaccination for all ages/sexes combined remain lower than expected based on cases of myocarditis/pericarditis in the population (CIHI-DAD/NACRS) adjusted for the age, sex and time to event distribution of the vaccinated population. When examined by age group and sex, the observed cases are still lower than expected. It is worthy of note that Canada is in the early stages of vaccinating younger Canadians, and few have received a second dose. With the inclusion of the additional cases (n=50), the observed count in males aged 12 to 17 seems to be higher than expected following Pfizer vaccination, although not statistically significantly higher. These data will continue to be examined closely as data are submitted over the next few weeks.

As of July 09, 2021, there were 111 cases of myocarditis reported to the Canada Vigilance database and the PHAC database. An increase in the observed vs expected cases was found to be statistically significant following the second dose of mRNA vaccines in younger male patients aged 12 to 17 years and 18 to 29 years.

End of Confidential Information

The detailed assessment of the 31 cases reported in the Canada Vigilance database is appended as part of the overall review of the risk of myocarditis and/or pericarditis following vaccination with mRNA vaccines. From this review, the majority of the reports were not medically

⁹¹ As per the data provided by the Public Health Agency of Canada (PHAC) Chief Public Health Officer Of Canada (CPHO) provided an updated report (included in Appendix 3)

⁹² As per the data provided by the Public Health Agency of Canada (PHAC) Chief Public Health Officer Of Canada (CPHO) provided an updated report (included in Appendix 3)

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confirmed as they were reported by consumers and with limited information to adequately assess the relatedness of the vaccines. Furthermore, the majority of the reports were from individuals who do not fall into the demographics of young males. Of note, the appended report does not include a causal assessment of the cases reported to the PHAC database.

6.1.2.4 International Cases

Israel (published on June 01, 2021⁹³)

- 275 cases of myocarditis were reported between December 2020 and May 2021
- Of these, 148 myocarditis cases have occurred around the time of vaccination
- 27 cases reported after first dose out of a total of 5,401,150 vaccinated individuals (of which 11 are vaccinated individuals with pre-existing conditions)
- 121 cases reported after second dose out of a total of 5,049,424 vaccinated individuals (of which 60 are vaccinated individuals with pre-existing conditions)
- The Israel Ministry of Health concluded to a possible link between the second vaccine dose and the onset of myocarditis among young men aged 16 to 30 years. A stronger link is observed among the younger age group, 16 to 19 years, compared to other age groups. In most cases, myocarditis took the form of a mild illness that resolved within a few days

MHPD comments: On June 01, 2021, Israel reported an incidence rate higher than the background rate^{94,95} in young male patients following vaccination. At that time, this finding had not been replicated elsewhere, but international regulatory agencies continued to actively monitor this event including emerging evidence. This information resulted in additional assessment internationally and in Canada.

United States

On May 24, 2021, the ACIP COVID-19 VaST Work Group reviewed the data on myocarditis and pericarditis⁹⁶ following mRNA COVID-19 vaccination reported to several United States databases. Data from the VAERS showed that within 30 days of receiving the second dose of either PFIZER-BIONTECH COVID-19 VACCINE or COVID-19 Vaccine Moderna, there was a higher number of observed than expected myocarditis and/or pericarditis cases in 16 to 24 year olds. The report was published on June 01, 2021 on the ACIP website.

⁹³ Surveillance of Myocarditis (Inflammation of the Heart Muscle) Cases Between December 2020 and May 2021 (Including) | Ministry of Health (www.gov.il)

⁹⁴ <https://www.gov.il/en/departments/news/01062021-03>

⁹⁵ <https://www.sciencemag.org/news/2021/06/israel-reports-link-between-rare-cases-heart-inflammation-and-covid-19-vaccination>

⁹⁶ COVID-19 VaST Technical Report May 24, 2021 | CDC

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On June 23, 2021, another ACIP meeting⁹⁷ was held. From this meeting, a higher prevalence of myocarditis cases was reported in younger male. The CDC⁹⁸ reported up to 166 cases of myocarditis in males aged 12 to 17 years per million vaccinated following the second dose of mRNA COVID-19 vaccination (~1:15,000 vaccinations), 56 cases per million in the 18 to 24 age group, and 20 cases per million in the 25 to 29 age group. For female, the highest reporting rate was amongst adolescent between 12 to 17 years of age (9.9 per million or ~1:100,000 vaccinations). A signal was identified in both male and female under 30 years of age following the second dose of mRNA vaccination.

As per the CDC in the United States, most confirmed cases have occurred mostly in male adolescents and young adults aged 16 years or older, more often after getting the second dose than after the first dose of one of the mRNA vaccine. The condition is typically seen within several days after COVID vaccination. These cases are rare in the context of global immunization when millions of vaccine doses have been administered. However, the ACIP concluded that the benefits outweigh the risks in the young populations. The CDC continues to recommend COVID-19 vaccination for everyone 12 years of age and older⁹⁹.

MHPD comments: From the ACIP meeting, data was presented indicating a higher incidence rate in adolescents and young adults. The observed vs expected rates showed a clear signal for myocarditis and pericarditis as they were much higher in younger age groups, especially after the second doses of mRNA vaccines. During the meeting, the U.S. FDA confirmed their intention to update the product information to include myocarditis and pericarditis for both mRNA COVID-19 vaccines.

Switzerland (Swissmedic) (published on June 04, 2021¹⁰⁰)

Spontaneous reports from Switzerland

- 5 million doses administered (as at the start of June 2021)
- Reported cases up to May 27, 2021:
 - 12 reports: Myocarditis (2), Perimyocarditis¹⁰¹ (4), Pericarditis (6)
 - Reporting rate 1:400,000 vaccine doses
 - Women (3), Men (8), Unk (1)
 - Average age 47 (range 18-70)
 - PFIZER-BIONTECH COVID-19 VACCINE (4), COVID-19 Vaccine Moderna (7), Unk (1)
 - After D1 (9), after D2 (3)

⁹⁷ ACIP June 2021 Presentation Slides | Immunization Practices | CDC

⁹⁸ Slide 29 (dataset up to June 11, 2021, Tom Shimabukuro, MD, MPH, MBA) from the Advisory Committee on Immunization Practices, June 23, 2021 ACIP June 23, 2021, CDC COVID-19 Vaccine Task Force

⁹⁹ <https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/myocarditis.html>

¹⁰⁰ Investigation of reports of myocarditis in connection with COVID-19 mRNA vaccines (swissmedic.ch)

¹⁰¹ With overlaps between these clinical presentations

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- Time to onset 8.75 days (range 1-28 days)
- 5/12 patients had a history of relevant illnesses (chronic kidney disease, kidney transplant, myelodysplastic syndrome, recurrent pericarditis (now with reported pericarditis after vaccination).
- 1/12 death reported (67 yo, M, pre-existing heart disease and renal failure requiring dialysis)
- *As can be ascertained from the documentation, most of the other patients experienced a fairly mild episode, or else the final details on the outcome of the illness are not yet available.*

MHPD comment On June 04, 2021, Swissmedic reiterated that the causality of the vaccine was still unclear in view of the reporting rate and low background incidence of the disease and the clinical complexity of the reported cases; however the agency committed to providing further information or introduce risk minimization measures if new information comes to light.

Singapore (HAS) published on June 11, 2021 (Expert Committee on COVID-19 Vaccination)¹⁰²

Spontaneous reports from Singapore

- 4 reports of myocarditis in young men
- Age range 18 to 30 years
- At the upper end of the expected range for this age group, based on background incidence rates
- Most cases occurred after a few days of the 2nd dose (D2)
- All have recovered or have been discharged well from hospital

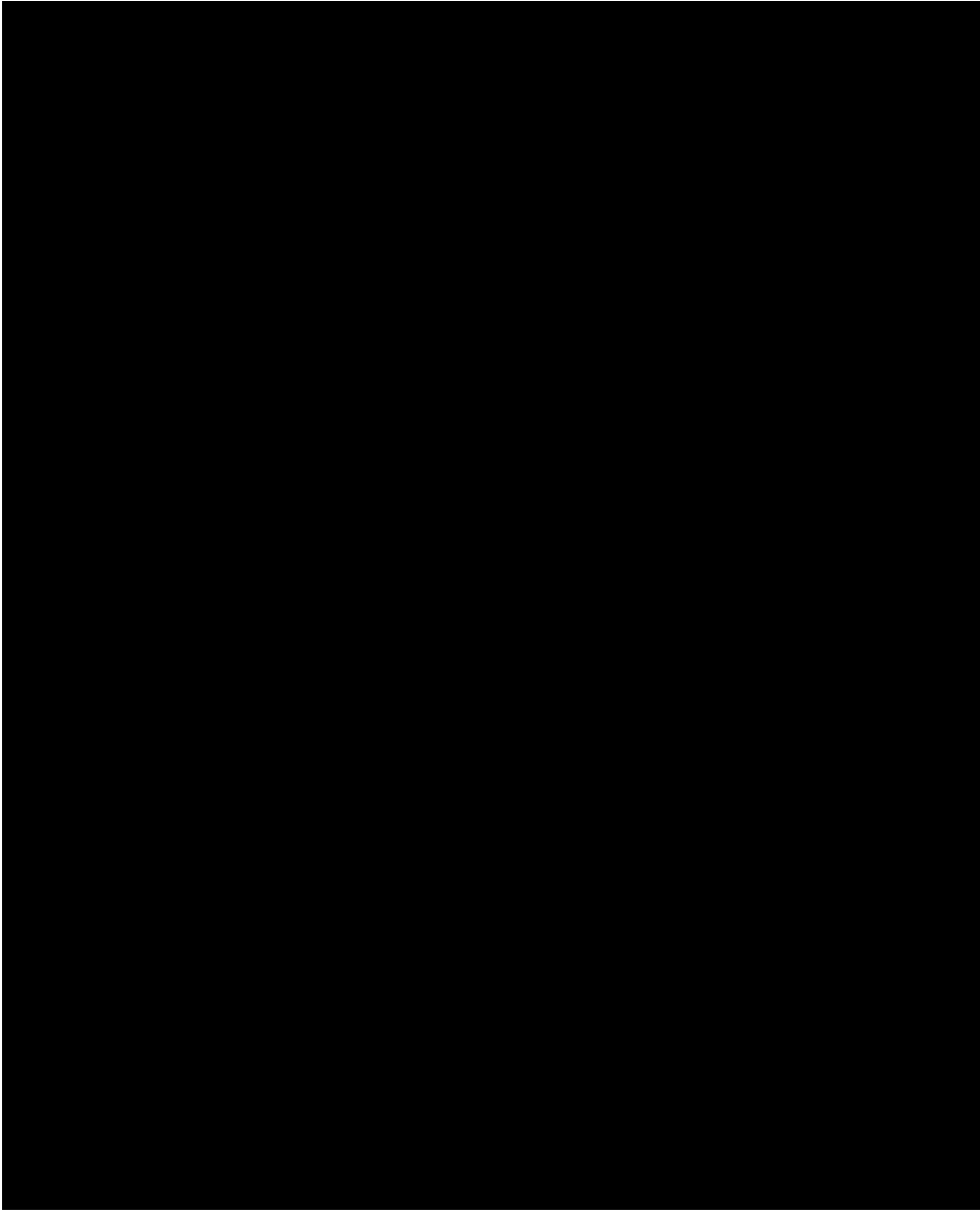
MHPD comments: Singapore concluded that there may be a very small risk of myocarditis and pericarditis after the second dose of an mRNA vaccine, particularly in young men. The national vaccine committee agency recommended that vaccinated persons, in particular adolescents and younger men, should avoid strenuous physical activity for one week after their second dose. The agency indicated that monitoring of the data was ongoing.

Overall, cases of myocarditis were being reported in several jurisdictions with data pointing to an increased reporting in young male patients following the second dose of mRNA vaccines

¹⁰² MOH | News Highlights

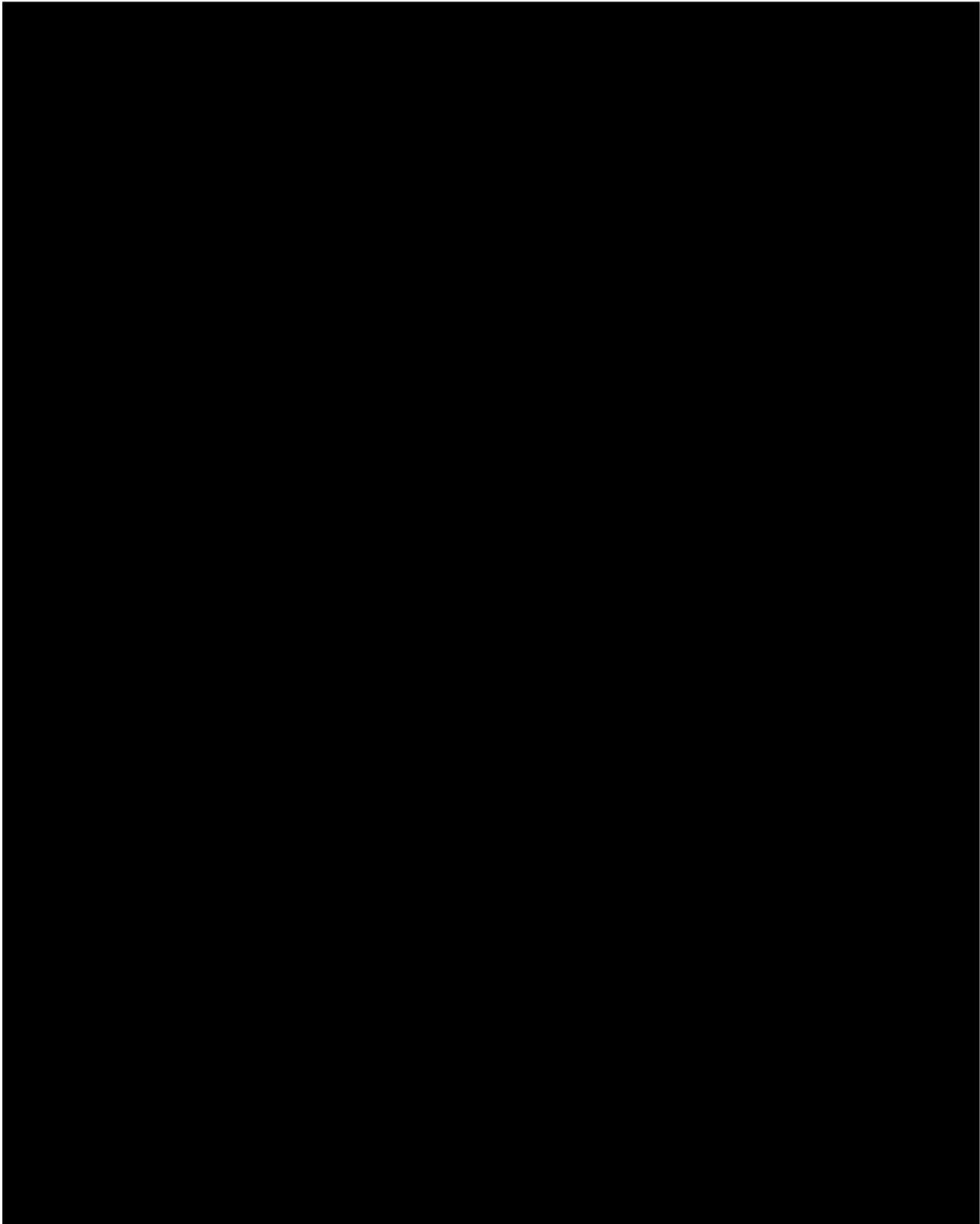
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EMA PRAC meeting

June meeting

- EMA data: based on Eudravigilance data assessment including an Observed/Expected analysis of myocarditis; a statistically disproportionate reporting was observed which was estimated to be 5 times higher in younger populations for all COVID vaccines. The signal was stronger in male; however, a signal was also detected in female of younger age groups.
- The EMA PRAC decided to initiate a safety signal regarding this risk with accelerated timelines.
- During the meeting, Israel shared their estimate incidence data: estimated incidence of myocarditis in the 16 to 19 years of age following vaccination is about 1 case in 6000 vaccinated individuals.
- Signal assessment will be separate from monthly safety report (with shorter timelines to be able to have maximal regulatory impact)-considerations to terms will be taken into account (myocarditis and or pericarditis)

July meeting

EMA O/E analysis myocarditis and pericarditis:

- Below 30 age group incidence rates: twice as high than older groups, majority of cases (75%) are for myocarditis
- When taking into account the myocarditis and pericarditis cases together the observed vs expected results are lower than when assessed separately.

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- O/E ratio comparable across vaccines:
 - Higher ratio in the below 30 age group
 - Results for Vaxevria are lower than those for Pfizer and especially lower than Moderna which has the highest ratios
 - Female group generally lower but absolute numbers are also lower.
 - Pediatric population no analysis because of lack of exposure data
- The EMA concluded to a causal association between the mRNA vaccines and myocarditis/pericarditis cases
- Following the completion of the signal assessment on myocarditis/pericarditis and mRNA vaccines, the EMA shared their proposed wordings with the MAHs. During the EMA PRAC meeting, Pfizer/BioNTech suggested changes to the proposed EMA updates and invited Dr Dror Mevorach to share the latest information from Israel as part of an oral explanation to the PRAC. Pfizer/BioNTech proposed to:
 - Include under 4.4 Warnings and Precautions that the course of myocarditis and pericarditis following vaccination *is typically mild and individuals tend to recover within a short time following standard treatment and rest*
 - Remove “myocarditis/pericarditis” from the adverse reactions section 4.8 *because data do not support causality*

Myocarditis/Pericarditis**Actions:**

- Labeling update (changes proposed by Pfizer during oral explanation not accepted). EMA maintained their recommendation for inclusion under 4.8 based on the signal assessment that had concluded to a causal association between myocarditis/pericarditis and mRNA vaccination.
- Include as Important identified risks in the RMPs for both mRNA vaccines MAHs
- List of follow-up questions to both mRNA vaccines MAHs.
- DHPC letter (joint letter to be issued later in July)
- Public Health Communication following PRAC
- The EMA PRAC also recommended convening an expert panel once more data is available to draft questions to the MAHs on risk factors to follow-up on this issue following the labeling update.

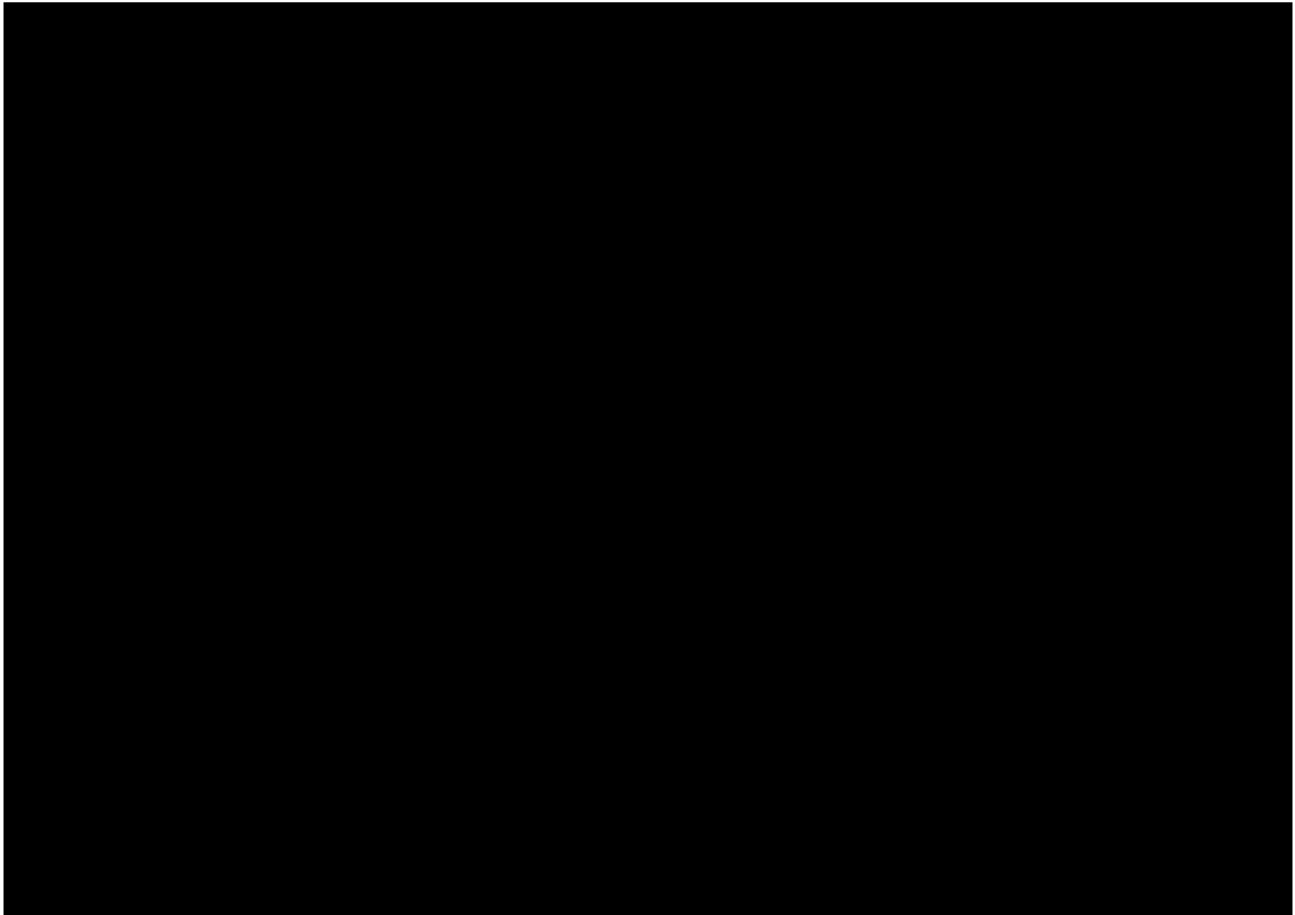
MHPD comments: The EMA PRAC requested the MAHs (Pfizer and ModernaTX, Inc.) to provide a detailed analysis of the myocarditis and pericarditis events following their May¹⁰³ meeting.

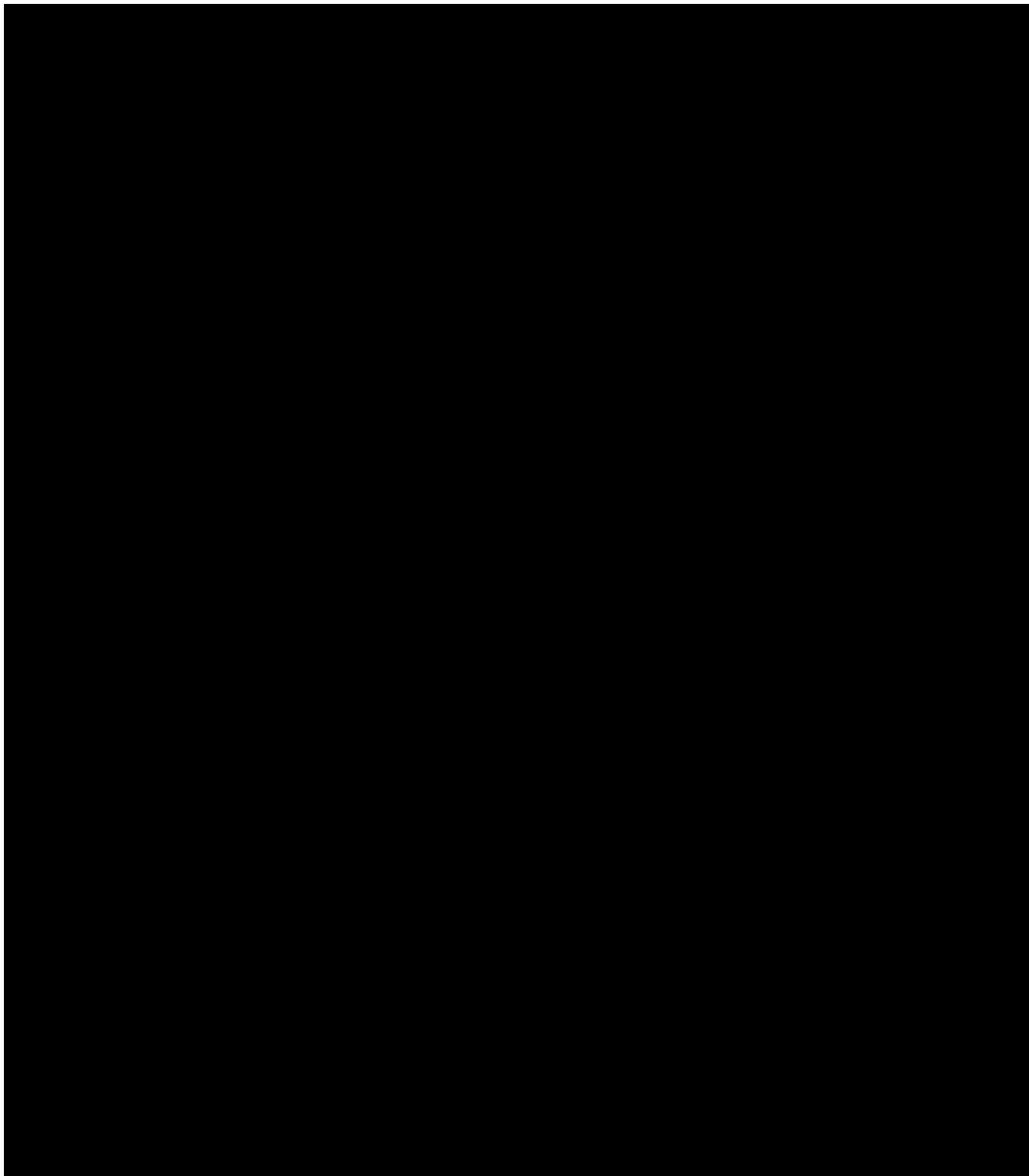
¹⁰³ <https://www.ema.europa.eu/en/news/meeting-highlights-pharmacovigilance-risk-assessment-committee-prac-3-6-may-2021>

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Following the EMA PRAC meeting on June 07, 2021, the agency recommended an accelerated timetable to assess the risk of myocarditis/pericarditis; the agency recommended assessing these events separately as different patterns seem to be emerging from these cases. Pericarditis cases tend to have more co-morbid conditions than myocarditis cases. The signal for myocarditis seems to be stronger when assessed separately from the pericarditis cases.

On July 09, 2021, the EMA PRAC, concluded to a possible link to very rare cases of myocarditis and pericarditis with mRNA COVID vaccines and updated the SmPCs of these products.





[REDACTED]

[REDACTED]

MHPD – PROTECTED B**REVIEW REPORT****End of Confidential Information****6.1.3 Scientific and medical literature***6.1.3.1 Analysis of Individual Case reports found in the literature*

A literature search of Embase was completed by the Health Library of Health Canada and the Public Health Agency of Canada on June 24, 2021. The keywords used in the search strategy were (1) “mRNA vaccines” and “pericarditis” and “myocarditis” which retrieved 40 references. Case reports of potential interest are discussed below:

1. Symptomatic Acute Myocarditis in Seven Adolescents Following Pfizer-BioNTech COVID-19 Vaccination (*Marshall et al, 2021*)¹⁰⁶

Summary

- 7 male patients (14 to 19 years old) (US)
- Myocarditis or myopericarditis 2-4 days after D2
- 6/7 no history of COVID-19 infection or another viral cause of inflammation
- Reported Symptoms: chest pain (7), fever (5), shortness of breath, fatigue, pain in both arms, nausea, vomiting, headache, anorexia and weakness
- Diagnosis: elevated troponin levels/abnormal electrocardiogram/cardiac MRI results
- Treatment: NSAIDs only (3), IV immune globin and corticosteroids (4)
- All recovered (within 2-6 days)
- Note (authors): Myocarditis onset shorter than myocarditis onset linked to smallpox vaccine

¹⁰⁵ Israel reports link between rare cases of heart inflammation and COVID-19 vaccination in young men | Science | AAAS ([sciencemag.org](https://www.sciencemag.org))

¹⁰⁶ Marshall M, Ferguson ID, Lewis P, et al. Symptomatic acute myocarditis in seven adolescents following Pfizer-BioNTech COVID-19 vaccination. *Pediatrics*. 2021; doi: 10.1542/peds.2021-052478 ([Case report](#))

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- Conclusion (authors): *Causality not established but temporal association with vaccination, striking similarity in the clinical and laboratory presentations raise the possibility for such a relationship*
2. Myocarditis after SARS-CoV-2 Vaccination: A Vaccine-induced Reaction? (D'Angelo et al, 2021)¹⁰⁷

Summary

- 30 year old male (Italy)
 - Myocardopericarditis 72 hours after D2 (given 21 days after D1)
 - Tested negative for COVID-19, family history negative for rheumatological or genetic diseases
 - Diagnosis: MRI/ECG and laboratory results
 - Treatment: bisoprolol and acetylsalicylic acid, prednisolone
 - Cardiac specific troponin levels progressively decreased, discharged home 7 days after hospitalization
 - Conclusion (authors): *in our case, we speculate that adverse reaction against the COVID-19 vaccine was responsible for the development of myocarditis due to its temporal relationship. However, substantial evidence other than temporal aspects still need to be provided to demonstrate causality, such as histologically proven cases of autoimmune myocarditis following vaccination.*
3. In Depth Evaluation of a Case of Presumed Myocarditis Following the Second Dose of COVID-19 mRNA Vaccine (Muthukumar et al, 2021)¹⁰⁸

Summary

- 50 year-old healthy male
 - Presumptive diagnosis of myocarditis 3 days after Dose 2 (COVID-19 Vaccine Moderna)
 - Conclusion (authors): *The case does not prove a causal association between the vaccine and the observed myocarditis-like syndrome. However, ischemic injury and other potential causes of acute myocardial injury were excluded, as were other potential infectious causes of myocarditis, and there was no evidence of systemic autoimmune disease. The lack of evidence for upregulation of IL17 cytokine, combined with the increased NK cell numbers observed in the case patient, could suggest a distinct vaccine-associated immunophenotype with a high likelihood for rapid recovery. However, it is not clear whether the observed differences reflect a potential (causal) pathologic immune response or rather appropriate healing responses to myocardial inflammation*
4. Myocarditis Temporally Associated with COVID-19 Vaccination (Rosner et al, 2021)¹⁰⁹

¹⁰⁷ Case report. Myocarditis after SARS-CoV-2 Vaccination: A Vaccine-induced Reaction?

¹⁰⁸ Case report. Presumed Myocarditis Following the Second Dose of COVID-19 mRNA Vaccine

¹⁰⁹ Case-serie (7 patients). Myocarditis after COVID-19 Vaccination

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- 7 male patients (US) below 40 years of age
- 6 patients received mRNA vaccines (COVID-19 Vaccine Moderna or Pfizer)
- Myocarditis 3-7 days post vaccination
- Symptoms: acute onset chest pain
- Diagnosis: elevated troponin, ECG and cardiac magnetic resonance
- Medical history: None had evidence of an active viral illness or autoimmune disease and 6/7 had negative PCR testing. Assessment of COVID19 serology was obtained for 6/7 patients, with 4/6 showing presence of spike protein IgG antibodies.
- Treatment varied and included beta-blocker and anti-inflammatory medication
- Outcome: all recovered/symptoms resolved following 3±1 days
- Conclusion (authors): *Our series of 7 male COVID-19 vaccination recipients who presented with myocarditis-like illness supports a potential causal association with vaccination given the temporal relationship, clinical presentation and CMR findings. The clinical course of vaccine-associated myocarditis-like illness appears favorable, with resolution of symptoms in all patients. Given the potential morbidity of COVID-19 infection even in younger adults, the risk-benefit decision for vaccination remains highly favorable.*

5. Myocarditis following COVID-19 mRNA vaccination (*Abu Mouch et al, 2021*)^{110,111}Summary:

- 6 male patients (median age 23 years)
- 5 patients presented after the second dose, 1 patient after the first dose of the BNT162b2 vaccine.
- Diagnosis: Myocarditis was diagnosed in all patients, there was no evidence of COVID-19 infection.
- Outcome: clinical course was mild in all six patients.
- Conclusion (authors): *An important consideration is a comparison of number of cases of suspected myocarditis post vaccination to the background rate of myocarditis. Our hospital serves a population of approximately 500,000 people. The mean number of myocarditis cases in winter months (December through March) for the past 5 years was 1.17 cases per month. Our six patients presented in less than a month period, indicating a higher rate. Our report of myocarditis after BNT162b2 vaccination may be possibly considered as an adverse reaction following immunization. We believe our information should be interpreted with caution and further surveillance is warranted.*

¹¹⁰ Short Communication: Myocarditis following COVID-19 mRNA vaccination (Israel)

¹¹¹ Abu Mouch S, Roguin A, Hellou E, et al. Myocarditis following COVID-19 mRNA vaccination. *Vaccine*. 2021;39(29):3790-3793. doi:10.1016/j.vaccine.2021.05.087

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6. Myocarditis following COVID-19 vaccination (*Albert et al, 2021*)¹¹²Summary

- 24 year-old male patient (healthy)
- Myocarditis based on Lake Louise Criteria (LLC)¹¹³ 4 days after D2
- Reported symptoms: fever, chills, and body aches in the first 24 hours after the shot
- Elevated troponin I (18.94ng/mL, normal 0.01- 0.04), elevated Creatine Kinase (704 U/L, normal 49-348), elevated C Reactive Protein (26.4 mg/L, normal <10.0) and negative PCR for COVID-19.
- Outcome: patient discharged with beta-blocker medication, instructed to avoid strenuous activities for three months. Patient has a scheduled follow-up appointment with cardiologist.
- Conclusion (authors): *We believe that given the negative PCR test for COVID-19, as well as the negative viral serologies, myocarditis, in this instance, was due to the vaccine, rather than acute infection, but the latter possibility cannot be totally discounted.*

MHPD comments: The vast majority the case reports on myocarditis were seen in males following the second dose of vaccination. All of the reported cases were serious. The vast majority of the cases recovered based on the outcome reported. No long-term follow-up of the cases is currently available. Some authors concluded a potential causal association with the vaccine based on the temporal relationship, clinical presentation and Cardiovascular Magnetic Resonance (CMR) imaging findings.

6.1.4 Public communication in Canada

On June 03, 2021, a Communiqué to Health Care practitioners was published on the government of Canada website¹¹⁴ indicating: international cases of myocarditis were observed and were more commonly reported after the second dose; Symptom onset was typically within several days after vaccination; Cases were mainly adolescents and young adults; Cases were more often males

¹¹² Albert E, Aurigemma G, Saucedo J, Gerson DS. Myocarditis following COVID-19 vaccination. *Radiol Case Rep.* 2021;16(8):2142-2145. doi:10.1016/j.radcr.2021.05.033

¹¹³ *In the original LLC, two out of three elements are needed for diagnosis. The three elements are: (1) regional or global myocardial signal intensity increase in T2-weighted images; (2) increased global myocardial early gadolinium enhancement ratio between myocardium and skeletal muscle in gadolinium-enhanced T1-weighted images; (3) at least one focal lesion with nonischemic distribution in late gadolinium enhancement. In the revised 2018 Lake Louise criteria, both (1) increased myocardial signal intensity ratio or increased myocardial relaxation times or visible myocardial edema in T2-weighted images and (2) increased myocardial relaxation times or extracellular volume fraction or late gadolinium enhancement in T1-weighted images are needed.*

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compared to females and cases experienced mild illness, responded well to conservative treatment and rest, and their symptoms improved quickly.

On June 24, 2021, a Health Product InfoWatch – June 2021 - Canada.ca was published on the Health Canada website regarding the risk of COVID-19 vaccines and reports of myocarditis and/or pericarditis.

On June 24, the British Columbia Centre for Disease Control published the details regarding the cases they had reported to the CAEFISS database in their Adverse Events Following Immunization with COVID-19 Vaccines report¹¹⁵. Of the 18 reports of pericarditis/myocarditis reported to the British Columbia Centre for Disease Control and medically evaluated *“Eight individuals had a diagnosis of pericarditis alone, four had myocarditis, and six had myopericarditis. Ages ranged from 16 to 95, and 12 were male. Six had received COVID-19 Vaccine Moderna, 10 had PFIZER-BIONTECH COVID-19 VACCINE, and two had AstraZeneca; two of the events occurred after a second dose (one PFIZER-BIONTECH COVID-19 VACCINE and one COVID-19 Vaccine Moderna). Some had alternate explanations including rheumatic diseases or genetic syndrome associated with cardiac disorders, **one case met the diagnostic criteria to be considered a definite case according to the draft Brighton Collaboration myocarditis case definition***

Concurrently, Hospitals in Ontario noted small emerging reports in the age 12 to 17 years group^{116,117}.

On June 30, Health Canada published a Public Advisory¹¹⁸ to inform the general public about the updates to the product monographs (labels) for the PFIZER-BIONTECH COVID-19 VACCINE and COVID-19 Vaccine Moderna to describe very rare reports of myocarditis and pericarditis following vaccination.

6.1.5 Updates to the Risk Management Plans

On June 07, 2021, Health Canada requested the MAHs to update the RMPs to include myocarditis/pericarditis as an important potential risk (Note: Approved RMPs included this risk as an important identified risk).

Health Canada issued an advisement letter to the MAHs (Pfizer Inc , HC6-024-e243022 (1.0) Reg Info - Health Product (DSTS control # 254161) and Moderna TX Inc HC6-024-e244946 (1.0) Reg Info - Health Product (DSTS control #254172) to include the risk of myocarditis and pericarditis following vaccination with the PFIZER-BIONTECH COVID-19 VACCINE or

¹¹⁶Reports of myocarditis/pericarditis after COVID-19 vaccination. SickKids Hospital-Clinical Considerations

¹¹⁷ SickKids reports seeing post-vaccine myocarditis in kids | Toronto Sun

¹¹⁸ <https://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2021/75959a-eng.php>

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COVID-19 Vaccine Moderna. The MAHs agreed with these requests and will submit changes for review.

7. Summary

The review of all of the information provided by MAHs and international partners (under confidentiality agreement) suggested that the benefits of the COVID-19 mRNA vaccines in preventing COVID-19 outweigh the risk of events of myocarditis/pericarditis. This is based on the following:

- The numbers of COVID-19 cases, hospitalization, and deaths continue to rise (Section 4.1).
- The COVID-19 mRNA vaccines along with the other approved COVID-19 vaccines are being used in combating the widespread threat of COVID-19 disease.
- Cases of myocarditis and/or pericarditis following immunization with COVID-19 vaccines have been reported in a small number of people in Canada and internationally. These reports are very rare. Health Canada and other international regulators are continuing to investigate the potential relationship between COVID-19 vaccines and these rare events.
- Most reported cases to date have followed vaccination with an mRNA vaccine based on an analysis of international cases, have occurred more often after the second dose and in younger male adults and adolescents. The Canadian evidence is expected to evolve as more people in these populations are vaccinated.
- Myocarditis/pericarditis following vaccination with an mRNA vaccine is mostly mild to moderate in severity, however severe and fatal cases can occur. The actual incidence is difficult to determine. Timely diagnosis and treatment may improve a patient's prognosis.
- Myocarditis/pericarditis following vaccination with mRNA vaccines was shown to resolve quickly with proper treatment; however, long-term sequelae in these cases is unknown. Tight follow-up and timely treatment may minimize this risk.
- This risk and the labelling changes have been communicated to the Canadian public through Infowatch and a public advisory.

8. Considerations:

There are remaining knowledge gaps including the exact mechanism of action of the myocarditis/pericarditis following vaccination and risk factors for risk minimization. In addition,

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available short-term follow-up data show that these events were typically mild and treatable; however, information on long-term outcomes is not yet available.

Health Canada will continue to expedite review of any emerging data as part of our enhance COVID-19 Vaccines safety monitoring.

9. Recommendations:

As part of safety monitoring and surveillance after post-authorization, the following recommendations should be considered.

For MHPD

- 1) Review the updated Risk Management Plans of the mRNA COVID-19 vaccines to ensure that the risk of myocarditis/pericarditis is adequately reflected
- 2) Continue monitoring these events especially in Canadian youth who are currently receiving their second doses of the mRNA vaccines.
- 3) Review post-market data submitted by the company (monthly safety report) and international information.
- 4) Communicate in a timely manner any additional regulatory changes/actions to health professional and vaccine recipient to ensure that relevant information is available.

10. References:

- Included as footnotes throughout the document

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11. Appendices:

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**Appendix 1: SPECIAL EXPERT MEETING ON VACCINE-ASSOCIATED
MYOCARDITIS/PERICARDITIS *Confidential Information***

Final Draft: Overview of discussion

**SPECIAL EXPERT MEETING ON VACCINE-ASSOCIATED
MYOCARDITIS/PERICARDITIS**

MS Teams meeting held on June 25th, 2021.

SUMMARY

- The objective of this meeting was to discuss the scientific evidence on rare cases of heart inflammation linked to immunization with mRNA COVID-19 vaccines.
- Rare cases of heart inflammation consistent with myocarditis and pericarditis have been reported internationally, mostly after the second vaccine dose. Symptoms generally manifested a few days post vaccination and were reported in all age groups, but predominantly in male adolescents and young adults. Pericarditis was seen across the age spectrum. Most cases resolved quickly with supportive treatment only. Because fewer young adults have been fully vaccinated with other types of COVID-19 vaccines, it is presently uncertain whether vaccine associated cardiac inflammation is specific to the mRNA platform.
- Early data in Canada suggest a similar signal associated with COVID-19 mRNA vaccines. Data are currently limited as many younger adults in Canada are only starting to get their second vaccine dose.
- The potential biological mechanisms underlying vaccine-associated myo/pericarditis are not currently known. Targeted biomedical and clinical research are needed to better understand disease pathophysiology and develop preventive and therapeutic measures.
- It is also important to determine whether COVID-19 vaccine-associated myocarditis is a feature specific to mRNA vaccines or whether similar side effects may be seen with other vaccine platforms.
- Active, coordinated and longer-term post vaccine surveillance, including prospective cohort studies that monitor cardiac and immune parameters is recommended.
- Clinical guidance for health care professionals is urgently required to effectively recognize and manage those affected and to counsel those potentially at higher risk.
- Balanced and transparent messaging to the general public and outreach to specific subgroups who may be at potential higher-risk for cardiac adverse effects is encouraged.
- The consensus view at this time is that the benefits of vaccination (prevention of COVID-19 infection and transmission as well as post-COVID complications such as long-COVID and MIS-C) outweigh the potential risk of vaccine-associated myo/pericarditis but that active monitoring and research are needed to understand and prevent vaccine-associated cardiac damage.

CHAIR:

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- Mona Nemer PhD, Chief Science Advisor of Canada

PARTICIPATING EXPERTS

- Natalia Abraham MD, FRCPC, Public Health Agency of Canada
- Gregor Andelfinger MD, PhD, CHU Sainte Justine
- Nagib Dahdah MD, FRCPC, University of Montreal
- Slava Epelman MD, PhD, FRCPC, Toronto General Hospital Research Institute
- Eleanor Fish PhD, University of Toronto
- Joanne Langley MD, MSc, FRCPC, Dalhousie University
- Peter Liu MD, FRCPC, University of Ottawa Heart Institute
- Brian McCrindle MD, FRCPC, Hospital for Sick Children
- Bruce McManus PhD, MD, FRSC, FCAHS, University of British Columbia
- Gavin Oudit MD, PhD, University of Alberta
- Caroline Quach MD, MSc, FRCPC, University of Montreal
- Manish Sadarangani BM, BCh, DPhil, University of British Columbia and BC Children's Hospital
- Marina Salvadori MD, Public Health Agency of Canada
- Supriya Sharma MD, Health Canada
- Matthew Tunis PhD, National Advisory Committee on Immunization
- André Veillette MD, Montréal Clinical Research Institute
- Bryna Warshawsky MD, Public Health Agency of Canada
- Rae Yeung MD, PhD, FRCPC, Hospital for Sick Children
- Joseline Zafack, MD, Public Health Agency of Canada

OTHER :

- Lori Engler-Todd MSc, Office of the Chief Science Advisor (**support**)
- Vanessa Sung PhD, Office of the Chief Science Advisor (**support**)
- Andreea-Diana Moisa BSc, Office of the Chief Science Advisor (**support**)

CONTEXT AND BACKGROUND:

- This special meeting was convened by the Chief Science Advisor of Canada to address emerging reports of rare cases of heart inflammation consistent with myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining around the heart) following administration of mRNA-based COVID-19 vaccines.
- The terms “myocarditis” and “pericarditis” are used in this summary with the acknowledgement that there are currently many unknowns about the nature of the inflammatory heart reactions following receipt of COVID-19 vaccines.
- Cardiac involvement including myocarditis has been previously reported in individuals infected with SARS-CoV-2 (Liu et al. *Circulation* 2020).
- Cardiac involvement including myocarditis, as part of a more generalized hyperinflammatory response termed MIS-C (multi-system inflammatory syndrome in children) has also been observed in children and young adults post-infection with SARS-CoV-2 (post-COVID condition)

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- Available international data, largely from the USA and Israel, suggest an association between mRNA vaccines and the reported cases of heart inflammation occurring predominantly in young males (12-29 year age group mostly).
- While the clinical outcome has typically been good, the potential long-term effects of vaccine-associated myocarditis/pericarditis are unknown. A better understanding of these conditions and who may be at higher risk is urgently needed.

SCIENTIFIC OBSERVATIONS: MYOCARDITIS AND PERICARDITIS FOLLOWING COVID-19 VACCINATION

Case surveillance

Most cases of myocarditis and pericarditis following COVID-19 vaccination have been reported from Israel and the US, two countries that are well along in the administration of the second dose of mRNA vaccines (Pfizer-BioNTech and Moderna) using the recommended three-four-week dose interval.

- Cases have been predominantly reported in younger males shortly following the second dose of mRNA vaccine (typically within four days). Clinical outcome has been good, (Marshall et al. Pediatrics 2021).
 - The Israeli Ministry of Health reported 121 cases out of ~ five million second doses within 30 days of vaccination.
 - Early data from the Vaccine Safety Datalink in the US reported 12.6 cases per million second dose of any mRNA vaccine within 21 days of vaccination (United States Centers for Disease Control and Prevention Advisory Committee on Immunization Practices meeting June 23, 2021).

In Canada, the National Advisory Committee on Immunization has recommended a complete series of Pfizer-BioNTech vaccination in everyone 12 years and older.

- In the 12 to 17 year old adolescent group, vaccination coverage is around 50% for dose one and 1% for dose two (Public Health Agency of Canada. Canadian COVID-19 vaccination coverage report, as of June 12, 2021).
- In the 18 to 24 year old young adult group, vaccination coverage is around 60% for dose one and 5% for dose two (Public Health Agency of Canada. Canadian COVID-19 vaccination coverage report, as of June 12, 2021).
- Dose intervals vary among provinces and territories, ranging from four to eight weeks, but most are using the same interval for both adults and adolescents.
- Early data in Canada suggests a possible safety signal in the 12 to 17 year old group who have received one dose of the Pfizer-BioNTech and Moderna vaccines. No signal has yet been detected in the 18 to 24 year old group, nor with the AstraZeneca viral vector vaccine.
- No information is available yet on related hospitalizations.

Case characteristics

Myocarditis can be caused by viruses (including SARS-CoV-2), bacteria, and toxins (Sagar et al. Lancet 2021; Liu et al. Circulation. 2020). The frequency of traditional *non-vaccine* associated myocarditis is estimated at approximately 2 per 100,000 people (Arness et al. Amer JEpi 2004) and is predominant in younger male individuals; the clinical course and outcomes are typically longer and more severe than

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what it is currently observed in cases associated with COVID-19 vaccines. Myocarditis has also been associated with smallpox vaccination (Engler RJM, et al. PLoS ONE 2015; Su et al. Vaccine 2021).

The frequency of COVID-19 *vaccine-associated* myo/pericarditis is currently under investigation. Patients presenting with this complication have been typically healthy individuals; only some (most have not) had previous SARS-CoV-2 infections (Shay et al JAMA Cardiology, 2021). Past infection by other agents is not known. An analysis (Liu et al, not yet published) of inflammatory heart reactions post-COVID-19 mRNA vaccination that have been reported to the World Health Organization's VigiBase and the US' VAERS systems found the following case characteristics:

- Cases reported after mRNA vaccines did not exceed those reported following influenza vaccines except among those 17 to 28 years of age. Cases in females appeared to be more evenly distributed across age groups.
- The most common symptoms were chest pain and elevated troponin levels.
- The cases that required hospitalization were characterized by short stays of about 2 to 3 days, and a good response to anti inflammatory medications such as non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and other immunosuppressive agents.
- As noted above, myocarditis was predominantly observed in young males in the 18-29 age group, was more common after a second dose of vaccine, with a typical symptom onset around day 3. Pericarditis cases were more often observed in individuals over 65 years of age.
- Fatal outcomes occurred (~1%) but tended to be in older individuals with comorbidities.

Hypotheses regarding triggers and potential biological mechanisms of vaccine-associated cardiac inflammation

Although cases of myo/pericarditis have been *associated* with COVID-19 vaccination, a *causal* link has not been established and the potential underlying biological mechanisms are not known. Of note, vaccine-associated myocarditis is distinct from viral myocarditis as no virus is found in the heart, but there is evidence of inflammation. Possible pathways or factors that could play a role in triggering inflammation of the heart and warrant further study were discussed. They include the **host immune response, vaccine dosage and interval, vaccine components and the role of sex hormones in cardiac manifestations**.

Host Immune response:

A role for the vaccine induced immune response is suggested by the following:

- Preliminary data indicate that myocarditis occurring after vaccination may reflect a dysregulated immune response. Perhaps as a consequence of RNA-recognition by pattern recognition receptors that lead to the production of type I interferons and other pro-inflammatory cytokines. The presence of fever, chills, myalgia occurring after receipt of mRNA vaccines, are highly suggestive of a heightened immune response.
- Children and youth typically display a more robust immune response in general, as compared to adults. This could be a possible explanation for why this age group is reporting more myocarditis following vaccination.
- Unlike “traditional” myocarditis caused by infection, children with COVID-19 vaccine-associated myocarditis respond dramatically and quickly to anti-inflammatory treatment, which further supports examining the immune response as a possible trigger.
- Previous SARS-CoV-2 infection may be a complicating factor and an indication of potential risk for vaccine-associated myocarditis. The infection may be a priming event that leads to an exaggerated immune response upon vaccination, noting that most cases have not had a previous .

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- Cases of vaccine-associated myocarditis in members of the same family suggest that genetic predisposition may play a role in a hyperactivated immune response to the vaccine.

Dose concentration and dose interval:

The vaccine dose concentration and the time interval between the first and second dose (dose interval) could also be relevant factors. The following should be considered:

- Dose concentration: As with other vaccines, adolescents are receiving the same dose of COVID-19 mRNA vaccines as adults. In Pfizer-BioNTech's clinical trial, adolescents 12 to 17 years of age mounted a stronger immune response compared to adults given the same dose of vaccine ([Frenck Jr. et al. NEJM 2021](#)). Pfizer-BioNTech is currently conducting clinical trials testing lower doses for children under 12 years of age. Of note, the Moderna COVID-19 vaccine which has about three times the mRNA concentration of the Pfizer-BioNTech COVID-19 vaccine (100 vs 30 micrograms) appears to be associated with higher incidence of myocarditis based on some analyses.
- Dose interval: The impact of the dose interval is presently unknown. Depending on the immunobiology mechanisms at play, longer intervals may decrease or increase vaccine-associated myocarditis. Data from Canada and the UK who have followed a longer dosing interval compared to Israel and the US may be informative. Different mechanisms of immune protection may be triggered after the first and second vaccine doses ([Sadarangani et al. Nat Rev Immunol 2021](#)).

Vaccine components:

It is also possible that distinct **components of mRNA vaccines** (mRNA containing modified nucleosides, lipid nanoparticles etc.) may be involved in the observed cardiac manifestations. This includes a possible role for the produced **spike protein** and/or its interaction with cardiac or vascular ACE2 receptors.

Sex differences:

The prevalence of myocarditis in **young males may reflect signal potentiation by male hormones or cardio protection by female hormones**. Estrogen has known cardiovascular protective effects. In the context of vaccine-associated myocarditis, a possible vascular or cardiac protective role for estrogen may explain the male prevalence. Interestingly, males affected by COVID-19 have a higher likelihood of severe disease than females; the role of sex hormones and sex chromosomes in cardiac inflammation and disease deserve further investigation. ([Viveiros et al. Am J Physiol Heart Circ Physiol. 2021](#)).

Knowledge gaps

Further research and data gathering are critical to address knowledge gaps and clarify the clinical picture of cardiac involvement associated with COVID-19 vaccines. Priority questions include:

1. What is the accurate estimation of the number of cases of myocarditis and pericarditis associated with COVID-19 vaccination and what are their distribution patterns across age groups and sex/gender? Is COVID-19 vaccine-associated cardiac disease a feature of the mRNA platform only?
2. Are there groups or individuals that may be potentially at higher risk of vaccine-associated heart disease and how should they be managed? For example:
 - i. Are young adults that were previously infected with COVID-19 at higher risk of myocarditis after receiving their first dose?
 - ii. Are children with documented Multisystem Inflammatory Syndrome (MIS-C) at elevated risk of vaccine-associated myocarditis? Prospective cohort studies of this group before they get vaccinated are particularly important.

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3. Are cardiac manifestations benign acute events or are there long-term impacts of vaccine-associated myocarditis especially in the young?
4. Why is heart inflammation more evident and are there subclinical injuries in other organs?

Priority Actions Moving Forward

The emerging issue of vaccine-associated heart disease requires attention on two important levels: addressing data and knowledge gaps on the one hand and promoting awareness and clinical care on the other.

Data and knowledge gaps

Myocarditis is clinically and pathologically defined as inflammation of the myocardium, but the causes of the inflammation can be numerous, and they influence treatment and prognosis (Sagar et al. Lancet 2012). Depending on disease severity and damage to the myocardium, such as myocyte loss and remodelling, myocarditis could have long term consequences including increasing susceptibility of the heart to other cardiotoxic agents and conditions. It is therefore **essential to understand the underlying mechanism of vaccine-associated myocarditis**.

1. Enhance knowledge of the frequency, epidemiology and clinical picture of mRNA vaccine-associated myocarditis. To enhance our knowledge of the frequency, epidemiology and clinical picture the following actions should be taken:

- i. **Rapidly set-up prospective cohort studies in paediatric and young adult populations to monitor cardiac and immune parameters in a longitudinal manner** complementing existing passive post vaccine surveillance efforts. Such studies would provide important health information for Canada and the world. This is best achieved by partnering with and enabling already established networks and funded programs in vaccine surveillance such as existing rheumatology/cardiology networks and infectious disease clinical networks across the country. Central coordination for the collection of all clinical data (including cardiac imaging) and biobanking of peripheral blood mononuclear cells (PBMCs), serum/plasma, is required. Some of this will be captured through current initiatives such as CANVAS-COVID and the routine AEFI surveillance system, but passive reporting systems may not pick up all cases nor provide needed longitudinal monitoring. Similarly, The Special Immunization Clinic network and Canadian Pediatric Society IMPACT study for hospital based surveillance will detect cases that come to medical attention in a hospital. The IMPACT network has started active surveillance with a rich clinical dataset for children admitted to 13 pediatric tertiary hospitals across Canada with AEFIs, including myocarditis – but their data will be restricted to those who are admitted to hospital in the pediatric (<17y) age group. Enabling expanded data capture together with standardized biospecimens at presentation with symptoms together with serial protocolized follow-up study will provide important information. In addition, there is a need to prospectively capture and follow a subgroup of children pre-first dose vaccine onwards in a uniform, serial and comprehensive manner. Additional research into familial adverse reactions could also help guide recommendations.
- ii. **Introduce a single case identifier via a centralized universal case depository platform to enhance the ability to combine and match knowledge.** Special requests would be needed from

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provincial healthcare programs to avoid duplicates on one hand, and to match clinical, biological, biobank, and genetic material on the other hand as several research projects may emerge.

- iii. **Using observational, lab based studies, and animal models, explore both the trigger (which component of the vaccine?) and the host response (immune and cardiac).** For now, the inflammatory complication appears to be more common with mRNA vaccines, and within the mRNA vaccines, more common with Moderna with higher mRNA load, but not with the viral vector platforms. However, it should be noted that fewer COVID-19 vaccines have been administered to younger age groups to-date. It is therefore important to determine whether vaccine-associated myocarditis is a feature specific to mRNA vaccines or whether similar side effects may be seen with other COVID-19 vaccines developed using different platforms when used in the younger age groups. In other words, is myocarditis due to RNA, lipid nanoparticles or the translated spike protein and/or its interaction with cardiac or vascular ACE2? Answers to these questions have significant implications for COVID-19 immunization and beyond. Experimental and clinical monitoring studies need to address the following issues, among others:

- **Understand the host immune response** (e.g. young male vs female, and the immune response after first dose vs second dose, considering the dose interval), and the immune imbalance inherent in the few individuals who develop the complications (e.g. innate immune genetic polymorphism). Information on immune response following the first dose in young males may be very helpful, as young male vaccinees may only need one dose.
- Determine whether the **inflammatory response is limited to the heart and pericardium** or whether **other organs are sub-clinically affected**, in which case, could this lead over time to other auto-inflammatory or auto-immune diseases as diabetes, psoriasis, atherosclerosis, etc.? In this respect, knowledge of the long-term impact of other vaccines associated myocarditis (e.g. smallpox) would be helpful. Severe cases with vaccine-associated systemic inflammation similar to a MIS-C phenotype have been reported, with multi-organ involvement.
- Determine if the **damage to the heart** is only transient or if there will be long-term subclinical or perhaps progressive damage leading to susceptibility to other cardiac diseases such as chronic cardiomyopathy, coronary artery disease, or arrhythmias.
- Understand the **immune basis underlying the myocarditis**. Is it auto inflammatory or auto immune? Innate or T cell mediated? Does it involve triggering of type I interferon by RNA? Could it be prevented by prophylactic and systematic administration of anti-inflammatory drugs such as nonsteroidal anti-inflammatory drugs in susceptible age groups, without compromising immune protection?
- Conduct SARS-CoV2 **infection studies using animal models** on the effects of the vaccines on expression of ACE2 in the heart, lung, kidney, intestine (other organs).
- **Learn more about MIS-C**. This may be the “tip of an iceberg” and lessons learned from the closest thing in the COVID pandemic is MIS-C.
- Develop a **long-term surveillance** sample to determine whether or not individuals who eventually become fully vaccinated would be at increased risk to develop myocarditis/pericarditis after exposure to classical causing agents (e.g., enteroviruses, coxsackie virus, etc.).

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2. Standardize and collect clinical data on a research basis

Standardized clinical research data should be collected as part of prospective cohort/research protocols:

- i. Extended bloodwork to interrogate the immune response, exposure to the virus and markers of myocardial damage, including:
 - Information relating to prior infection - asymptomatic or symptomatic - collected on all cases of vaccine-induced myocarditis using antibody assays.
 - Circulating levels of IFN-alpha/beta, IL-1 β and IL-6 (plasma/serum).
 - Activation status of CD8 and CD4 T cells, B cells, macrophages, natural killer (NK) and dendritic cells.
 - Duration of any aberrant cytokine response or inappropriate immune cell activation.
 - Serial troponin measurement (along side with comprehensive SARS-CoV2 serology) after 1st and 2nd vaccination in two cohorts
 - A) children/young adults considered totally healthy
 - B) those who have had some evidence of an adverse response to prior COVID infection – for example, COVID19 toes.
 - A further cohort study of those who meet criteria for myocarditis with standardized follow-up to determine the spectrum and relevance of this issue, as well as any non-cardiac morbidities.
- ii. **Follow kids prospectively for adverse events** through App-based monitoring, and recruit based on symptoms (both with and without symptoms).
 - Kits can be sent to patients, and returned by mail. With a single blood finger prick, ten proteins can be measured – e.g. troponin, antibody and inflammatory markers.

Communication and clinical care

1. Identify groups at higher risk that could benefit from better follow-up or alternative approaches.

The data so far indicate that males and those in a younger age group may be at risk for the rare cardiac events. **Further research and longer-term data gathering are required to identify populations who may be at higher risk. In the meantime, the following groups may benefit from closer follow ups:**

- Those with a previous diagnosis of MIS-C or myo/pericarditis post first vaccine dose.
- Those with autoimmune peri/myocarditis (small but well known population of patients followed by rheumatology/immunology) – isolated single organ autoimmunity, as well as those suffering from it due to an underlying autoimmune disease i.e. systemic lupus erythematosus (SLE), vasculitis, arthritis, autoinflammatory disease, etc.
- Male adolescents who are immunocompromised and experiencing pro-inflammatory disease exacerbation, during a flare or acute phase.

The following actions would help **clarify who is most at risk:**

- Adopting a standard case definition (suggest using [Brighton collaboration](#)).
- Developing an agreed upon process for investigation and follow-up that is child-appropriate as well as adult appropriate – and could be used in a variety of settings, including rural and remote locations.
- Coordinating with international monitoring efforts.

2. Provide targeted public communication and outreach to healthcare professionals

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Overall, myocarditis is a rare complication associated with COVID-19 mRNA vaccines. While the longer term consequences are not yet known, the consensus view of the experts, based on the rapid recovery of most individuals, is that the benefits of vaccination programs outweigh the risks at a population level, particularly as SARS-CoV-2 infection itself and associated MIS-C carry a much higher risk of myocardial injury (Liu et al. *Circulation* 2020) and long-term sequelae. Transparent **targeted communication and outreach** regarding myocarditis and pericarditis following COVID-19 vaccination are essential as science evolves, and should include:

- Transparent public communication to inform the **general public and potentially susceptible populations of frequency, symptoms and management of vaccine induced cardiac disease** without negatively impacting vaccine acceptance.
- Separate and appropriate **outreach, communications, and guidance to healthcare providers** so that they are prepared to care for patients who present with vaccine-associated cardiac disease. Among other:
 - Health professionals should be alerted to the unique presentation, natural history, potential management strategies and also the risk for rare adverse outcomes of these inflammatory complications, to further minimize downstream negative impact. This includes paediatricians, family and emergency physicians.
 - Canadian cardiology, rheumatology/immunology and infectious disease societies could work together to develop common guidelines for investigation and care management, to be promoted as a best practice. Of note, a multi-disciplinary group at the Hospital for Sick Children has developed a preliminary guidance document for health care professionals with plans in place for multi-pronged knowledge dissemination, including engaging the Canadian Pediatric Society. The document could be used as a basis, expanding guidance to adult populations.
 - The Government of Canada should provide evidence-based messaging linking to speciality society recommendations.

Postscript

- Following the expert meeting discussion, some noteworthy developments have occurred :
 - On June 25th, the United States Food and Drug Administration added a warning about the risk of myocarditis and pericarditis to fact sheets for Moderna and Pfizer-BioNTech COVID-19 vaccines. They advise vaccine recipients to seek medical attention right away if they have chest pain, shortness of breath, fast-beating, fluttering or pounding heart after vaccination.
 - On June 30th, Health Canada issued updates to the product monographs for Pfizer-BioNtech and Moderna COVID-19 vaccines for myocarditis and also issued a public advisory.
 - COVID-19 vaccines continue to be recommended for all eligible individuals, including youth.
 - On July 6, the US Centres for Disease Control and Prevention (CDC) published a Morbidity and Mortality Weekly Report (MMWR) pre-report “*Use of mRNA COVID-19 Vaccine After Reports of Myocarditis Among Vaccine Recipients: Update from the Advisory Committee on Immunization Practices (ACIP)— United States, June 2021*” noting that ACIP concluded that the benefits of COVID-19 vaccination to individual persons and at the population level clearly outweighed the risks of myocarditis after vaccination. This followed the June 23, 2021, US CDC ACIP meeting to discuss myocarditis after mRNA vaccines.

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- Abbasi, J. Researchers Investigate What COVID-19 Does to the Heart. JAMA Network (2021). 325(9). <https://doi:10.1001/jama.2021.0107>
- Dennis, A et al. Multiorgan impairment in low-risk individuals with post-COVID-19 syndrome: a prospective, community-based study. BMJ Open (2021). 11(3). <https://doi:10.1136/bmjopen-2020-048391>
- Fox, SE et al. COVID-19 Myocarditis: Quantitative analysis of the inflammatory infiltrate and a proposed mechanism. Cardiovascular Pathology (2021). <https://doi.org/10.1016/j.carpath.2021.107361>
- Grimaud, M et al. Acute myocarditis and multisystem inflammatory emerging disease following SARS-CoV-2 infection in critically ill children. Annals of Intensive Care (2020). 10(69). <https://doi.org/10.1186/s13613-020-00690-8>
- Habib, MB et al. Acute myocarditis following administration of BNT162b2 vaccine. IDCases (2021). <https://doi.org/10.1016/j.idcr.2021.e01197>
- Kim HW, et al. Patients With Acute Myocarditis Following mRNA COVID-19 Vaccination. JAMA Cardiol (2021). <https://doi:10.1001/jamacardio.2021.2828>
- Mansour, J et al. Acute myocarditis after a second dose of the mRNA COVID-19 vaccine: a report of two cases. Clinical Imaging (2021). <https://doi.org/10.1016/j.clinimag.2021.06.019>
- Marshall, M et al. Symptomatic Acute Myocarditis in Seven Adolescents Following Pfizer-BioNTech COVID-19 Vaccination. Pediatrics (2021). <https://doi.org/10.1542/peds.2021-052478>
- Mei, R et al. Myocarditis and pericarditis after immunization: Gaining insights through the Vaccine Adverse Event Reporting System. International Journal of Cardiology (2018). <https://doi.org/10.1016/j.ijcard.2018.09.054>
- Minosha, KP et al. Recurrence of Acute Myocarditis Temporally Associated With Receipt of the mRNA COVID-19 Vaccine in an Adolescent Male. The Journal of Pediatrics (2021). <https://doi.org/10.1016/j.jpeds.2021.06.035>
- Montgomery J, et al. Myocarditis Following Immunization With mRNA COVID-19 Vaccines in Members of the US Military. JAMA Cardiol (2021). <https://doi:10.1001/jamacardio.2021.2833>
- Muthukumar, A et al. In Depth Evaluation of a Case of Presumed Myocarditis Following the Second Dose of COVID-19 mRNA Vaccine. Circulation (2021). <https://doi.org/10.1161/CIRCULATIONAHA.121.056038>
- Sadarangani, M., et al. Immunological mechanisms of vaccine-induced protection against COVID-19 in humans. Nat Rev Immunol (2021). <https://doi.org/10.1038/s41577-021-00578-z>
- Shay DK, et al. Myocarditis Occurring After Immunization With mRNA-Based COVID-19 Vaccines. JAMA Cardiol (2021) . <https://doi:10.1001/jamacardio.2021.2821>
- Viveiros A et al. Sex differences in COVID-19: candidate pathways, genetics of ACE2, and sex hormones. Am J Physiol Heart Circ Physiol (2021). 320. <https://doi.org/10.1152/ajpheart.00755.2020>
- Zeng, YY et al. COVID-19 and the cardiovascular system. Nature Reviews Cardiology (2020). 17(5). <https://doi.org/10.1038/s41569-020-0360-5>

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Appendix 2. FDA's EUA updates on Myocarditis and Pericarditis Confidential Information

FDA's changes to the EUA documents for providers and patients incorporating the information on myocarditis/pericarditis shared under mutual confidentiality agreement on June 25, 2021.

USPI-courtesy copy enclosed below:



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Appendix 3. CPHO Myocarditis Update June 29, 2021 Confidential Information

Myocarditis/Pericarditis AEFI Reports - Canada

Data up to and including June 25, 2021

Canadian update

Up to and including June 25, 2021, a total of **90** cases of myocarditis/pericarditis following administration with a COVID-19 vaccine have been reported to PHAC and Health Canada – **64 following Pfizer vaccination** (Table 1) and 25 following vaccination with other COVID-19 vaccines. One additional case is missing vaccine type. Currently, the majority of myocarditis cases following the Pfizer vaccination are after dose #1, and the rate per 100,000 doses administered is the same after dose #1 and #2 (Table 2). Just over half the cases are in females with a median age of 42 years.

The observed cases of myocarditis/pericarditis cases following vaccination for all ages/sexes combined remain lower than expected based on cases of myocarditis/pericarditis in the population (CIHI-DAD/NACRS) adjusted for the age, sex and time to event distribution of the vaccinated population (Table 3). When examined by age group and sex, the observed cases are still lower than expected (Table 4). It is worthy of note that Canada is in the early stages of vaccinating younger Canadians, and few have received a second dose.

A preliminary, supplementary analysis on additional cases of myocarditis/pericarditis from P/Ts that have not yet been submitted or reviewed by PHAC are included in the Appendix. With the inclusion of the additional cases (n=50), the observed count in males aged 12 to 17 seems to be higher than expected following Pfizer vaccination, although not statistically significantly higher. These data will continue to be examined closely as data are submitted over the next few weeks.

Table 1: Cases of myocarditis/pericarditis, by vaccine, based on cases reported to the Canadian Adverse Events Following Immunization Surveillance System (CAEFISS) and Canada Vigilance Database (CVD) for COVID-19 Vaccines up to and including June 25, 2021¹.

Vaccine trade name	# of cases	Doses administered ⁵	Rate per 100,000 doses administered (CI) ⁶
Pfizer²	64	23,769,463	0.27 (0.21-0.34)
Dose #1	40	18,376,037	0.22 (0.16-0.30)
Dose #2	12	5,423,684	0.22 (0.11-0.39)
Moderna³	18	5,987,684	0.30 (0.18-0.48)
Dose #1	9	4,490,110	0.20 (0.09-0.38)
Dose #2	7	1,365,854	0.51 (0.21-1.06)
COVISHIELD/AstraZeneca⁴	7	2,596,923	0.27 (0.11-0.56)

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Dose #1	6	2,198,688	0.27 (0.10-0.59)
Dose #2	0	398,247	0 (0-0.75)

¹One case missing vaccine type.

²Twelve cases missing dose number for Pfizer.

³Two cases missing dose number for Moderna.

⁴One case missing dose number for COVISHIELD/AstraZeneca.

⁵Doses administered as of June 19, 2021 (June 20, 2021 for Quebec).

⁶Confidence interval (CI) calculated using the Poisson exact method.

Draft Canadian background rates (CIHI – DAD/NACRS) – Annual: 24 per 100,000 persons per year (broad); 14 per 100,000 persons per year (narrow).

Table 2: Cases of myocarditis/pericarditis following **Pfizer/BioNTech** vaccination, based on cases reported to the Canadian Adverse Events Following Immunization Surveillance System (CAEFISS) and Canada Vigilance Database (CVD) for COVID-19 Vaccines up to and including June 25, 2021¹.

	Pfizer/BioNTech					
	# cases	Dose number ²	Rate per 100,000 doses administered	Median Age ³ (range)	Sex	Median Time to onset (range)
Myocarditis/ pericarditis	64	40 following dose #1 12 following dose #2	0.27 for both doses 0.22 for dose #1 0.22 for dose #2	42 (15-86) y/o	34 females; 30 male	8 days (5 hours to 92 days)
Total Doses Administered⁴	23,769,463					

¹All PT terms under the HLGT terms “Myocardial disorders” and “Pericardial disorders” were used to pull the data.

²Dose number missing for twelve cases.

³Age is missing for three cases.

⁴Doses administered as of June 19, 2021 (June 20, 2021 for Quebec).

MHPD – PROTECTED B**REVIEW REPORT****Table 3:** Observed vs Expected¹ myocarditis/pericarditis by time to event, data as of June 25, 2021 – all ages/sexes².

Vaccine trade name	Observed ³ (CI)*	Expected, time at risk = 30 days ⁴ (CI)**
Pfizer/BioNTech	62 (47.54-79.48)	587.85 (565.88 - 610.49)
Moderna	18 (10.67-28.45)	160.09 (154.3 - 166.05)
COVISHIELD/AstraZeneca	7 (2.81-14.42)	74.01 (71.5 - 76.59)

¹Only cases that had a vaccine trade name were included in the observed counts. Reports were excluded if time to onset was greater than 30 days. Reports with missing time to onset were included in this analysis.

²Most recent doses administered data as of June 19, 2021.

³Observed data as of June 25, 2021.

⁴Broad definition includes the following ICD-10-CA codes: 109.0 (Rheumatic myocarditis), 130.x (Acute pericarditis), 131.x (Other diseases of the pericardium), 132.x (Pericarditis in disease classified elsewhere), 140.x (Acute myocarditis), 141.x (Myocarditis in disease classified elsewhere), 151.4 (Myocarditis, unspecified).

*95% confidence intervals for observed events were calculated using the Poisson exact method.

**95% confidence intervals for the number of expected events were calculated using the Poisson exact confidence intervals around the age and sex specific background rates.

Please note: Parts of this material are based on data and information compiled and provided by CIHI. However, the analyses, conclusions, opinions and statements expressed herein are those of the author, and not necessarily those of CIHI.

Source: Discharge Abstract Database and National Ambulatory Care Reporting System, Canadian Institute for Health Information, Fiscal years 2014-2019, CAEFISS database, Canada Vigilance database.

Table 4: Myocarditis/pericarditis - Observed vs Expected¹ age groups and sex, by vaccine trade name^{2,3} using a time at risk of 30 days.

Vaccine trade name	Age (years)	Males		Females	
		Observed ⁴ (CI)*	Expected (CI)**	Observed ⁴ (CI)*	Expected (CI)**
Pfizer[^]	12 to 17	6 (2.20-13.06)	7.35 (6.81 - 7.91)	1 (0.03- 5.57)	2.75 (2.42 - 3.11)
	18 to 24	2 (0.24-7.22)	22.53 (21.7 - 23.4)	1 (0.03- 5.57)	9.04 (8.45 - 9.66)
	25 to 39	10 (4.80-18.39)	51.44 (50.04 - 52.86)	9 (4.12- 17.08)	25.92 (24.84 - 27.03)

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Moderna[†]	12 to 17	0 (0-3)	0.03 (0.03 - 0.03)	0 (0-3)	0.01 (0.01 - 0.01)
	18 to 24	2 (0.24-7.22)	7.24 (6.97 - 7.52)	1 (0.03-5.57)	2.59 (2.42 - 2.76)
	25 to 39	9 (4.12-17.08)	17.17 (16.7 - 17.64)	1 (0.03-5.57)	7.28 (6.98 - 7.6)
COVISHIELD/AstraZeneca	12 to 17	0 (0-3)	0 (0-0)	0 (0-3)	0 (0-0)
	18 to 24	0 (0-3)	0.11 (0.10-0.11)	0 (0-3)	0.04 (0.03-0.04)
	25 to 39	0 (0-3)	1.05 (1.03 - 1.08)	0 (0-3)	0.34 (0.33-0.36)

[†]Only cases with vaccine trade name, age and sex were included in the observed counts. Reports were excluded if time to onset was greater than 30 days. Reports with missing time to onset were included in this analysis.

²Based on broad observed/expected definition. Broad definition includes the following ICD-10-CA codes: *I01.0 (Acute rheumatic pericarditis), I01.2 (Acute rheumatic myocarditis), I09.0 (Rheumatic myocarditis), I09.2 (Chronic rheumatic pericarditis), I30.x (Acute pericarditis), I31.x (Other diseases of the pericardium), I32.x (Pericarditis in disease classified elsewhere), I40.x (Acute myocarditis), I41.x (Myocarditis in disease classified elsewhere), I51.4 (Myocarditis, unspecified).*

³Most recent doses administered data as of June 19, 2021.

⁴Observed data as of June 25, 2021.

[^]18 of 29 cases age 12 to 39 following Pfizer were 1st dose.

[†]7 of 14 cases age 12 to 39 following Moderna were 1st dose.

*95% confidence intervals for observed events were calculated using the Poisson exact method.

**95% confidence intervals for the number of expected events were calculated using the Poisson exact confidence intervals around the age and sex specific background rates.

Please note: Parts of this material are based on data and information compiled and provided by CIHI. However, the analyses, conclusions, opinions and statements expressed herein are those of the author, and not necessarily those of CIHI.

Source: Discharge Abstract Database and National Ambulatory Care Reporting System, Canadian Institute for Health Information, Fiscal years 2014-2019, CAEFISS database, Canada Vigilance database.

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In an effort to obtain a close-to-real time view of this issue, provincial and territorial vaccine safety officials were asked to provide to PHAC information on all active cases of myocarditis/pericarditis up to June 28. In response, several provinces submitted their current myocarditis/pericarditis case counts to PHAC (n=50 additional cases). Tables A1 and A2 show the observed/expected analyses with these additional cases included. Provincial cases that did not have age or sex were excluded from the analyses. Please note that not all of the cases have been entered or medically reviewed by PHAC. Some cases may be duplicates.

Table A1: Observed vs Expected¹ myocarditis/pericarditis by time to event, data as of June 28, 2021 – all ages/sexes².

Vaccine trade name	Observed ³ (CI)*	Expected, time at risk = 30 days ⁴ (CI)**
Pfizer/BioNTech	106 (86.78-128.2)	587.85 (565.88 - 610.49)
Moderna	29 (19.42-41.65)	160.09 (154.3 - 166.05)
COVISHIELD/AstraZeneca	14 (7.65-23.49)	74.01 (71.5 - 76.59)

¹Analysis includes all possible reports from P/Ts up to and including June 28, 2021. Some cases have not been reviewed at the provincial/federal level and there may be duplicates. Only cases that had a vaccine trade name were included in the observed counts. Reports were excluded if time to onset was greater than 30 days. Reports with missing time to onset were included in this analysis.

²Most recent doses administered data as of June 19, 2021.

³Observed data as of June 28, 2021.

⁴Broad definition includes the following ICD-10-CA codes: I01.0 (Acute rheumatic pericarditis), I01.2 (Acute rheumatic myocarditis), I09.0 (Rheumatic myocarditis), I09.2 (Chronic rheumatic pericarditis), I30.x (Acute pericarditis), I31.x (Other diseases of the pericardium), I32.x (Pericarditis in disease classified elsewhere), I40.x (Acute myocarditis), I41.x (Myocarditis in disease classified elsewhere), I51.4 (Myocarditis, unspecified).

*95% confidence intervals for observed events were calculated using the Poisson exact method.

**95% confidence intervals for the number of expected events were calculated using the Poisson exact confidence intervals around the age and sex specific background rates.

Please note: Parts of this material are based on data and information compiled and provided by CIHI. However, the analyses, conclusions, opinions and statements expressed herein are those of the author, and not necessarily those of CIHI.

Source: Discharge Abstract Database and National Ambulatory Care Reporting System, Canadian Institute for Health Information, Fiscal years 2014-2019, CAEFISS database, Canada Vigilance database.

Table A2: Myocarditis/pericarditis - Observed vs Expected¹ by 10 year age groups and sex, by vaccine trade name^{2,3} using a time at risk of 30 days.

Vaccine trade name	Age (years)	Males	Females

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		Observed ⁴ (CI)*	Expected (CI)**	Observed ⁴ (CI)*	Expected (CI)**
Pfizer[^]	12 to 17	12 (6.20-20.96)	7.35 (6.81 - 7.91)	1 (0.03-5.57)	2.75 (2.42 - 3.11)
	18 to 24	6 (2.20-13.06)	22.53 (21.7 - 23.4)	4 (1.09-10.24)	9.04 (8.45 - 9.66)
	25 to 39	14 (7.65-23.49)	51.44 (50.04 - 52.86)	10 (4.8-18.39)	25.92 (24.84 - 27.03)
Moderna[†]	12 to 17	0 (0-3)	0.03 (0.03 - 0.03)	0 (0-3)	0.01 (0.01 - 0.01)
	18 to 24	2 (0.24-7.22)	7.24 (6.97 - 7.52)	1 (0.03-5.57)	2.59 (2.42 - 2.76)
	25 to 39	10 (4.80-18.39)	17.17 (16.7 - 17.64)	2 (0.24-7.22)	7.28 (6.98 - 7.6)
COVISHIELD/AstraZeneca	12 to 17	0 (0-3)	0 (0-0)	0 (0-3)	0 (0-0)
	18 to 24	0 (0-3)	0.11 (0.10 - 0.11)	0 (0-3)	0.04 (0.03 - 0.04)
	25 to 39	1 (0.03-5.57)	1.05 (1.03 - 1.08)	0 (0-3)	0.34 (0.33 - 0.36)

¹Analysis includes all possible reports from P/Ts up to and including June 28, 2021. Some cases have not been reviewed at the provincial/federal level and there may be duplicates. Only cases with vaccine trade name, age and sex were included in the observed counts. Reports were excluded if time to onset was greater than 30 days. Reports with missing time to onset were included in this analysis.

²Based on broad observed/expected definition. Background rates for myocarditis/pericarditis - broad include the following ICD-10-CA codes: I01.0 (Acute rheumatic pericarditis), I01.2 (Acute rheumatic myocarditis), I09.0 (Rheumatic myocarditis), I09.2 (Chronic rheumatic pericarditis), I30.x (Acute pericarditis), I31.x (Other diseases of the pericardium), I32.x (Pericarditis in disease classified elsewhere), I40.x (Acute myocarditis), I41.x (Myocarditis in disease classified elsewhere), I51.4 (Myocarditis, unspecified).

³Most recent doses administered data as of June 19, 2021.

⁴Observed data as of June 28, 2021.

[^]33 of 47 cases age 12 to 39 following Pfizer were 1st dose.

[†]8 of 15 cases age 12 to 39 following Moderna were 1st dose.

*Confidence intervals for observed events were calculated using the Poisson exact method.

**Confidence intervals for the number of expected events were calculated using the Poisson exact confidence intervals around the age and sex specific background rates.

Please note: Parts of this material are based on data and information compiled and provided by CIHI. However, the analyses, conclusions, opinions and statements expressed herein are those of the author, and not necessarily those of CIHI.

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Source: Discharge Abstract Database and National Ambulatory Care Reporting System, Canadian Institute for Health Information, Fiscal years 2014-2019, CAEFISS database, Canada Vigilance database.

International update¹¹⁹**Table 5: Myocarditis/pericarditis cases reported internationally*.**

Myocarditis and pericarditis						
Country	Vaccine	Dose	Ages	Rate per 100,000 (95% CI, if available)	Signal declared?	Data source
USA (up to May 31, 2021)	mRNA	Post-2 nd dose	12 to 15	2.24	No	https://www.fda.gov/media/150054/download
			16-17	3.5		
			18-24	2.06		
			25-39	0.5		
			40-49	0.3		
			50-64	0.13		
			65+	0.09		
	Pfizer	Post-1 st dose	16-39	0.12 (0-0.66)		
		Post-2 nd dose		1.04 (0.43 to 2.15)		
(up to May 29 th , 2021)	Moderna	Post-1 st dose		0.52 (0.11 to 1.51)		
		Post-2 nd dose		2.47 (1.23 to 4.41)		

¹¹⁹ Please note that the rates presented in the "International update" are crude rates.

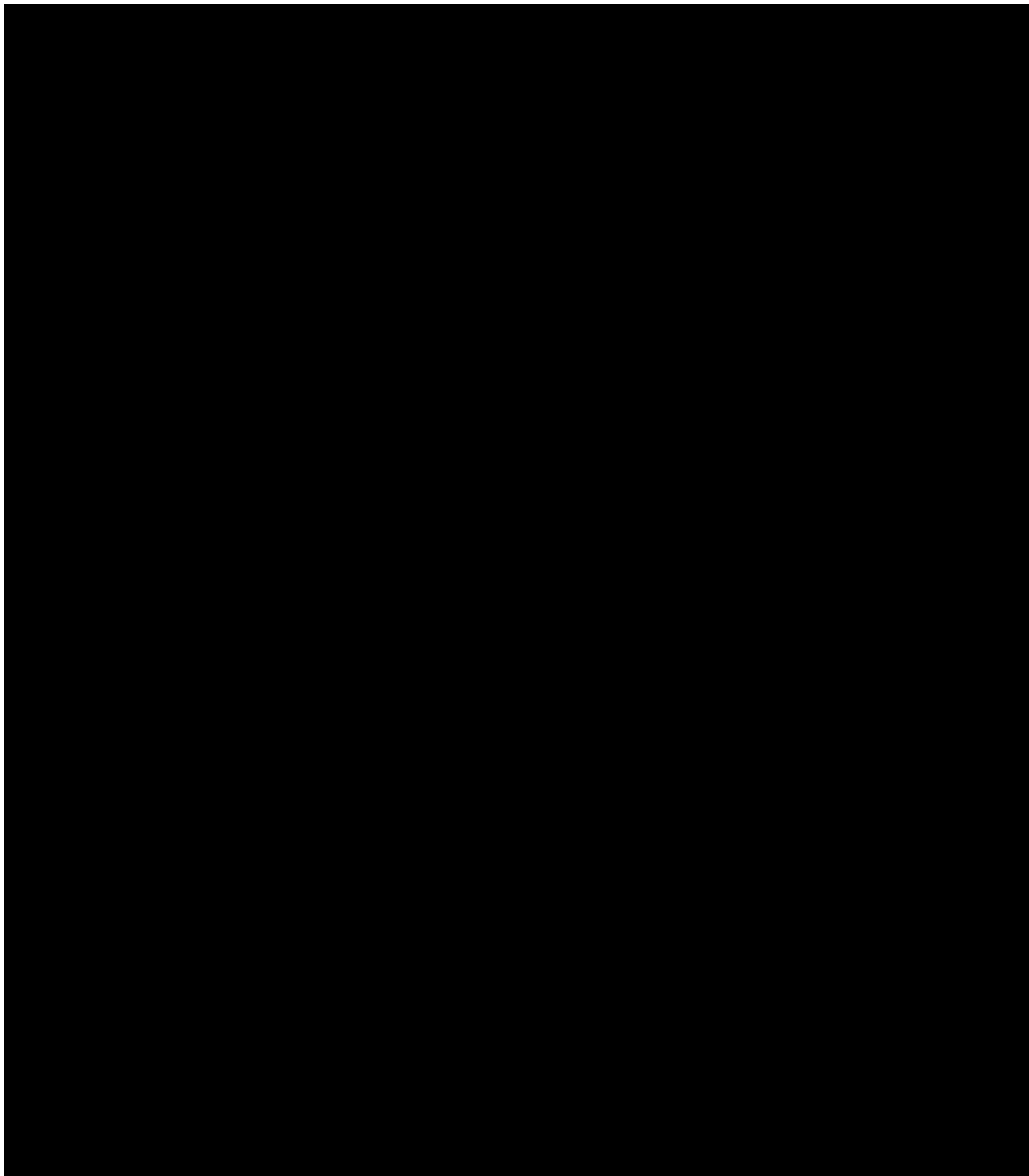
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France (up to June 10, 2021)	Pfizer	All doses	All eligible ages	0.33		https://ansm.sante.fr/uploads/2021/06/18/20210618-covid-vaccins-fiche-synthese-04-06-2021-10-06-2021-2.pdf
	Moderna	All doses		0.23		
Germany (up to May 31, 2021)	Pfizer	Not specified	All eligible ages	0.13 (0.1 to 0.17) to 0.42 (0.32 to 0.55)		Paul-Ehrlich-Institut - Dossier Coronavirus SARS-CoV-2 and COVID-19 Coronavirus and COVID-19 (pei.de)
	Moderna			0.11 (0.04 to 0.26) to 0.35 (0.11 to 0.81)		
Norway (up to June 15, 2021)	Pfizer	Post-1 st dose	All eligible ages	1.83		Reported suspected adverse reactions coronavirus vaccines as of May 25 2021.pdf (legemiddelverket.no)
		Post-2 nd dose		2.65		
	Moderna	Post-1 st dose		2.09		
		Post-2 nd dose		1.86		
	AZ	Post-1 st dose		0.73		
UK (up to June 9 th , 2021)	Pfizer	Post-1 st dose	All eligible ages	0.42		COVID-19 mRNA Pfizer-BioNTech Vaccine Analysis Print.pdf (publishing.service.gov.uk)
		Post-2 nd dose		0.61		
	AZ	Post-1 st dose		0.37		COVID-19 AstraZeneca Vaccine Analysis Print.pdf (publishing.service.gov.uk)
		Post-2 nd dose		0.54		

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						COVID-19 vaccine weekly safety report - 10-06-2021 Therapeutic Goods Administration (TGA)
Australia (up to June 13, 2021)	Pfizer	Not specified	All eligible ages	0.75		COVID-19 vaccine weekly safety report - 17-06-2021 Therapeutic Goods Administration (TGA)
New Zealand (up to May 15, 2021)	Pfizer	Not specified		0.83		Safety Report #11 – 15 May 2021 (medsafe.govt.nz)
Switzerland (up to June 4, 2021)	mRNA	Not specified	All eligible ages	0.25		Investigation of reports of myocarditis in connection with COVID-19 mRNA vaccines (swissmedic.ch)
Israel (up to May 31, 2021)	Pfizer	Post-1 st dose	All eligible ages	0.5	Yes	Surveillance of Myocarditis (Inflammation of the Heart Muscle) Cases Between December 2020 and May 2021 (Including) Ministry of Health (www.gov.il)
		Post-2 nd dose		2.4		

*Data presented in Table 5 is from the previous week (June 22, 2021).



MHPD – PROTECTED B**REVIEW REPORT****Questions for all agencies:**

3. Has your agency received any case-reports of myocarditis following Covid-19 immunisation, particularly for Comirnaty (Pfizer) or Moderna-vaccine?
If yes, could you provide further details on these cases?
4. Did your agency evaluate, or are you planning to extensively evaluate the risk (signal) of myocarditis with Covid-19 vaccines?
5. If any conclusions regarding this potential risk have already been reached by your agency, could you share the evaluation-results in this IPMS-round?

Health Canada Response:

1. *Has your agency received any case-reports of myocarditis following Covid-19 immunisation, particularly for Comirnaty (Pfizer) or Moderna-vaccine? If yes, could you provide further details on these cases?*

There have been 21 cases of myocarditis/pericarditis following vaccination with Pfizer-BioNTech COVID-19 vaccine (18 cases) or Moderna COVID-19 vaccine (3 cases) in Canada as of May 25, 2021. A summary of the Canadian adverse event following immunization (AEFI) reports is posted online on a weekly basis, which can be accessed here: <https://health-infobase.canada.ca/covid-19/vaccine-safety/>.

Information on these cases is summarized below:

		Pfizer-BioNTech	Moderna
Sex	Female	13	0
	Male	5	3
Age (Years)	Adult (18-49)	8	3
	Adult (50-64)	6	0
	Elderly (65+)	2	0
	Unknown	2	0
Time to onset (Range)		5 hours – 94 days	1 – 8 days
Medical History/ Concomitant medications		13 cases had underlying medical conditions (Asthma, Drug allergy, Psoriatic arthritis,	2 cases had underlying medical conditions (ADHD, cardiac

MHPD – PROTECTED B**REVIEW REPORT**

		Diabetes, Hypertension, Environmental allergy, Chemical sensitivity, Gluten intolerance, Psoriasis, Endometriosis, Migraine, Schizoaffective disorder, Premenstrual dysphoric disorder (PMDD), Chronic migraines, Seasonal allergies, Herpes simplex type I, Raynaud's phenomenon, NASH (Nonalcoholic Steatohepatitis), Hypertension, diabetic, asthma, fibromyalgia (reported as fibro), COVID-19 prior to vaccination, Type 2 diabetes, blocked artery)	neoplasm, and open heart surgery)
Outcome	Recovered/resolved	2	2
	Not recovered/not resolved	3	0
	Not yet recovered	8	1
	Recovered/resolved with sequelae	1	0
	Recovering/resolving	2	0
	Unknown	2	0
Doses aministered as of May 15, 2021		11,781,796	3,171,023
Reporting rate per 100,000 doses administered		0.153	0.095

2. Did your agency evaluate, or are you planning to extensively evaluate the risk (signal) of myocarditis with Covid-19 vaccines?

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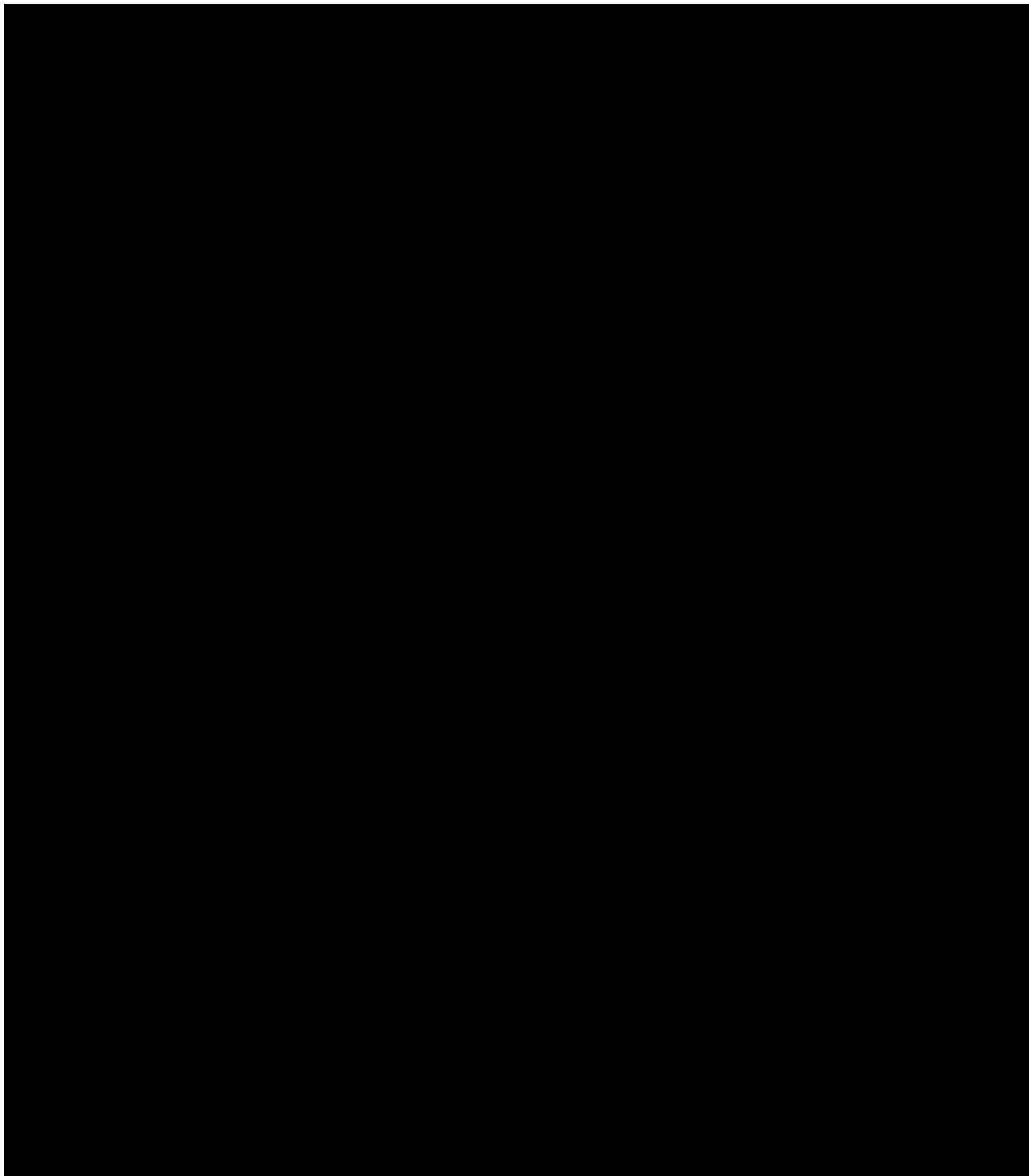
The cases of myocarditis reported in the monthly safety reports for Pfizer BioNtech (#5) and Moderna (#4) are currently under review. In addition, all cases reported in our surveillance systems continue to be collected and reviewed regularly.

3. *If any conclusions regarding this potential risk have already been reached by your agency, could you share the evaluation-results in this IPMS-round?*

At this time, no conclusions regarding this potential risk have been reached by Health Canada. The review is ongoing and will continue to share information as needed.

[REDACTED]

[REDACTED]



[REDACTED]

[REDACTED]



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Marketed Health Products Directorate
Health Products and Food Branch Health Canada

Medical Ad Hoc Review
COVID 19 Vaccines
Myocarditis/Pericarditis

Bureau

Date:[Completion date of the report]

Security – Classification – de sécurité:
Protected B (when completed)

Inclusion of confidential information (i.e., shared by another regulatory agency) into the assessment should be clearly identified (highlighted) and should be included if considered necessary.



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Canada

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ISSUE(S) AND PURPOSE

Evaluation of this issue was initiated as a result of reports from Israel regarding myocarditis in young males after Pfizer COVID vaccination in May 2021. Subsequently there was a statement from CDC regarding myocarditis in young males. A detailed review of international evaluation and statements is available in the report prepared by the MHPD scientists. Currently there is concern related to both myocarditis and pericarditis. As of July 2021 it appears that there is a signal of myocarditis in young males (age 18-26 approximately) This has lead a number of regulatory authorities to consider product labelling for the mRNA COVID 19 Vaccines. There is interest to determine if there are adequate Canadian cases to compel labelling for some or all COVID 19 vaccines. This review covers all cases submitted to Canada Vigilance up to July 16, 2021

BACKGROUND

Pfizer prepared a detailed safety report on myocarditis/pericarditis. The following is extracted from this report (May 2021)

“Myocarditis is an inflammation of the heart muscle that may present with chest pain, palpitations, arrhythmias and/or heart failure. It may occur in children and adults and is more common in young men than young women. An estimated global prevalence of myocarditis is 22 cases per 100,000 patients. Diagnostic work-up may include serum cardiac biomarkers such as troponins and creatine kinase, electrocardiogram, echocardiography, cardiovascular magnetic resonance imaging and endomyocardial biopsy (diagnostic gold standard). Etiologies can include infection (most commonly viral), autoimmune (e.g. sarcoid and systemic lupus erythematosus) and drugs or toxins. In 50% of cases, acute myocarditis resolves quickly within 2-4 weeks, however 25% may develop persistent cardiac dysfunction and 25% may deteriorate to end-stage dilated cardiomyopathy. Treatment is dependent on presentation and may be directed at a specific etiology, if determined, heart failure and arrhythmias, if present.¹²³

Pericarditis is an inflammation of the pericardial sac that contains the heart and fixes it to the mediastinum. Males between 20-50 appear to be at highest risk for pericarditis. The incidence has been reported to be about 28 cases per 100,000 in an urban Italian area. Diagnosis of acute pericarditis is made if 2 of 4 clinical criteria are met: 1. Pericardial chest pain, 2. Pericardial rub on auscultation, 3. ECG changes, 4. Pericardial effusion. Etiologies can remain unknown in 40-85% of patients with pericarditis but may be microbial (most commonly viral > bacterial) or autoimmune (e.g. systemic lupus erythematosus, rheumatoid arthritis) or neoplastic. It can be self-limiting or complicated by pericardial effusion and constriction (tamponade). Treatment is directed at inflammation with colchicine or other NSAIDs, aspirin, corticosteroids and anakinra (IL-1 receptor antagonist). Recurrences occur in about 30% of patients.⁴

Myocarditis is not a common feature of COVID-19 but has been reported in case reports and case series. Ho et. al reviewed the literature for cases of myocarditis post COVID 19 and found 51 patients:

12 with confirmed (by cardiac magnetic resonance imaging or endomyocardial biopsy) and 39 with possible (cardiac biomarkers, ECG and/or echocardiograms) myocarditis. Patients had a median age of 55 and 69% were male. In general, they presented with the range of symptoms seen in myocarditis of other etiologies. Mortality was 27%.”

Ad Hoc Review

Product and Signal

A more detailed review is available in the Ad-Hoc Report: messenger ribonucleic acid (mRNA) COVID-19 Vaccines PFIZER-BIONTECH COVID-19 VACCINE and COVID-19 Vaccine Moderna Myocarditis/Pericarditis SAP #3013445

REVIEW

As of July 16, 2021 there are 37 reports in the Canada Vigilance Database. This includes 4 duplicates so this review is for 33 unique reports. Seven cases were either medically confirmed or the individual who experienced the adverse event was a physician, in 4 cases information regarding medical confirmation was not available, in 22 cases the reporter was a consumer and was not medically confirmed.

This review does not include cases reported to CAEFISS. PHAC has provided regular reports that address these cases and the most recent reports are attached as appendices. Of note, the PHAC reports include both Canada vigilance and CAEFISS reports so some of the information provided below is incorporated into their summary reports. (Appendix A)

Pericarditis

There are 20 unique reports (Pfizer 13, Moderna 6, AstraZeneca 1).

Of the 13 Pfizer reports: females 8, males 5; median age 47 (range 22-72); dose 1 (6) dose 2 (4) dose unknown (3)

WHO causality: probable 2, possible 6, unlikely 3, unassessable 2

Brighton criteria classification (Appendix B): level 1-0, level 2-1, level 3-0, level 4-6, level 5-6

(of note, the level 2 report is for a 24 year old female who developed symptoms after dose 2 of Pfizer vaccine)

Of the 6 Moderna reports: females 3, males 1, unknown 1; median age 29 (range 20-61); dose 1 (3) dose 2 (3)

WHO causality: probable 1, possible 2, unlikely 1, unassessable 2

Brighton criteria classification: level 1-0, level 2-1, level 3-0, level 4-2, level 5-3

(of note, the level 2 report is for a 20 year old female who developed symptoms after dose 2 of Moderna vaccine)

There was also a single report after Astra Zeneca vaccine: 48 year old female after dose 1; WHO classification possible, Brighton criteria classification level 4

Myocarditis

There are 14 unique reports with one case reporting both myocarditis and pericarditis which is the report after vaccination with Astra Zeneca described above. (Pfizer 9, Moderna 3, not specified 1)

Of the 9 Pfizer reports: females 4, males 5; median age 38 (range 23-68); dose 1 (6) dose 2 (1) dose unknown (2)

WHO causality: probable 2, possible 4, unlikely 2, unassessable 1

Brighton criteria classification: level 1-0, level 2-3, level 3-0, level 4-4, level 5-2

(of note, the level 2 reports are as follows: 38 year old male who developed symptoms after dose 1; 68 year old female whose symptoms occurred after unknown dose; 55 year old female who developed symptoms after dose 1)

Of the 3 Moderna reports: females 1, males 2; ages 55, 62, not reported; dose 1 (2), dose 2 (1)

WHO causality: possible 1, unlikely 1, unassessable 1

Brighton criteria classification: level 1-0, level 2-0, level 3-0, level 4-2, level 5-1

SUMMARY

There are currently 3 COVID 19 vaccines administered in Canada. These are 2 mRNA vaccines manufactured by Pfizer and Moderna and one viral vector vaccine manufactured by Astra Zeneca. Another viral vector vaccine manufactured by COVISHIELD is not currently administered in Canada. In addition, a viral vector vaccine manufactured by Janssen (Johnson and Johnson) is approved but not yet distributed in Canada.

Initial reports from Israel of myocarditis in young males alerted medical regulatory authorities to a potential concern. Subsequent reports of both myocarditis and pericarditis in the USA and to the EMA as well as in other countries raised additional concerns. This ad hoc review focuses on 33 reports reported to Canada Vigilance.

Up to July 16, Canada Vigilance has received unique reports with more reports of pericarditis than myocarditis. The majority of these reports are from consumers and not medically confirmed. This results in limited data and limited quality of the reports, affecting the ability of Health Canada reviewers to draw conclusions or assess causality between the vaccines and the adverse event. In addition, the majority of the reports are for individuals who do not fall into the demographics of young males. As a result, the data from Canada Vigilance reports is of very limited value in signal assessment. Combination of CV and PHAC data may allow signal detection.

RECOMMENDATIONS

1. Continue to review cases of potential myocarditis/pericarditis as received
2. Recognize the limited value of consumer reports for meaningful signal detection and consider new approaches to including these reports in signal detection
3. Support PHAC as the lead for the issue of myocarditis and pericarditis as a potential/confirmed signal
4. Use PHAC data as supporting data if there is a decision for a label change
5. Recognize that there is no need for additional detailed external communication on this issue since health care professionals and Canadian consumers have been well informed about this issue unless there is significant new information which would impact the administration of the vaccines or the treatment specific to post-vaccine myocarditis or pericarditis.

Appendix A

Myocarditis/Pericarditis AEFI Reports - Canada

Data up to and including July 16, 2021

Canadian update

Up to and including July 16, 2021, a total of **211** cases of myocarditis/pericarditis following administration with a COVID-19 vaccine have been reported to PHAC and Health Canada – **132 following Pfizer vaccination, 66 following Moderna and 12 following COVISHIELD/AstraZeneca** (Table 1). One additional case is missing vaccine type.

Currently, most myocarditis cases following the Pfizer vaccination are after dose #1 and just over half the cases are in males with a median age of 38 years (Table 2). Conversely, most myocarditis cases following Moderna are after dose #2, and the majority are male, and the median age is 29. The median time to onset is 6 days for Pfizer, 3 days for Moderna. The time to onset is shorter for dose #2 vs. dose #1.

For all ages and sexes together, the observed number of myocarditis/pericarditis cases following Pfizer and mRNA together, are lower than expected for 7 and 21 days at risk (Table 3). Of note, the top row in the observed cases includes all myocarditis/pericarditis cases that have been coded and reviewed in CAEFISS/CVD. The bottom row includes all cases in CAEFISS/CVD **PLUS** early alert cases that have been emailed to PHAC by the jurisdiction. The additional, early alert, cases (n=135) have not been medically reviewed at PHAC and may contain errors or duplicates. These data will continue to be examined closely as data are submitted over the next few weeks.

Focusing on CAEFISS and CVD cases, and adjusting for the sequential nature of the analyses, the following groups have an observed count significantly greater than expected at the 1% significance level:

- **Males 18-29 following dose #2 of Moderna**
- **Males 18-29 following any dose of Moderna** (using 7-day time at risk only)
- **Males 18-29 following mRNA dose #2** (using 7-day time at risk only)

Table 1: Cases of myocarditis/pericarditis, by vaccine, based on cases reported to the Canadian Adverse Events Following Immunization Surveillance System (CAEFISS) and Canada Vigilance Database (CVD) for COVID-19 Vaccines up to and including July 16, 2021¹.

Vaccine trade name	# of cases	Doses administered ⁵	Rate per 100,000 doses administered (CI) ⁶
Pfizer²	132	29,570,445	0.45 (0.37-0.53)
Dose #1	76	18,911,572	0.40 (0.32-0.50)
Dose #2	36	10,622,916	0.34 (0.24-0.47)
Moderna³	66	10,457,774	0.63 (0.49-0.80)

Dose #1	19	5,121,856	0.37 (0.22-0.58)
Dose #2	37	5,168,758	0.72 (0.50-0.99)
mRNA (Pfizer and Moderna)	198	40,028,219	0.49 (0.43-0.57)
Dose #1	95	24,033,428	0.40 (0.32-0.48)
Dose #2	73	15,791,674	0.46 (0.36-0.58)
COVISHIELD/AstraZeneca⁴	12	2,752,733	0.44 (0.23-0.76)
Dose #1	9	2,203,229	0.41 (0.19-0.78)
Dose #2	1	534,281	0.19 (0.00-1.04)

¹One case missing vaccine type.

²Twenty cases missing dose number for Pfizer.

³Ten cases missing dose number for Moderna.

⁴Two cases missing dose number for COVISHIELD/AstraZeneca.

⁵Doses administered as of July 10, 2021 (July 11, 2021 for Quebec).

⁶Confidence interval (CI) calculated using the Poisson exact method.

Draft Canadian background rates (CIHI – DAD/NACRS) – Annual: 24 per 100,000 persons per year (broad); 14 per 100,000 persons per year (narrow).

Table 2: Cases of myocarditis/pericarditis following **mRNA** vaccination, based on cases reported to CAEFISS and CVD for COVID-19 Vaccines up to and including July 16, 2021^{1,2}.

	mRNA vaccination						
	Total doses administered ²	Dose #	# of cases	Rate per 100,000 doses administered (CI)	Median age (range)	Sex	Median time to onset (range)
Pfizer/ BioNTech	29,570,445	Both	132	0.45 (0.37-0.53)	39 (12-86) y/o	61 females 70 males	6 days (4 hours to 92 days)
	18,911,572	1	76	0.40 (0.32-0.50)	38 (12-86) y/o	39 females 37 males	6.5 days (4 hours to 72 days)
	10,622,916	2	36	0.34 (0.24-0.47)	39 (16-82) y/o	17 females 19 males	4 days (1 day to 91 days)
Moderna	10,457,774	Both	66	0.63 (0.49-0.80)	31 (18-95) y/o	19 females 45 males	3 days (1 hour to 69 days)

Ad Hoc Review

Product and Signal

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	5,121,856	1	19	0.37 (0.22-0.58)	35 (21-95) y/o	6 females 13 males	6 days (1 hour to 46 days)
	5,168,758	2	37	0.72 (0.50-0.99)	29 (18-72) y/o	10 females 27 males	2 days (7 hours to 28 days)

¹All PT terms under the HLGT terms “Myocardial disorders” and “Pericardial disorders” were used to pull the data.

²Cases with missing sex, dose number, age, and time to onset were excluded from the analysis.

³Doses administered as of July 10, 2021 (July 11, 2021 for Quebec).

Table 3: Myocarditis/pericarditis reports to CAEFISS and CVD, Observed vs Expected^{1,2} by time to event and vaccine type, data as of July 16, 2021, all ages/sexes.

Vaccine trade name	Doses admin	Time at risk = 7 days			Time at risk = 21 days		
		Observed ⁴ (CI)*	Expected (CI)**	Rate (per 100,000 doses admin)	Observed ⁴ (CI)*	Expected (CI)**	Rate (per 100,000 doses admin)
Pfizer/ BioNTech	29,570,445	67 (51.92 - 85.09)	203.22 (196.45 - 210.19)	0.23	98 (79.56 - 119.43)	567.66 (548.68 - 587.13)	0.33
		89 (71.47 - 109.52)		0.30	127 (105.87 - 151.11)		0.43
Moderna	10,457,774	53 (39.70 - 69.33)	71.62 (69.27 - 74.04)	0.51	60 (45.79 - 77.23)	184.96 (178.89 - 191.18)	0.57
		89 (71.47 - 109.52)		0.85	99 (80.46 - 120.53)		0.95
mRNA	40,028,219	120 (99.49 - 143.49)	274.83 (265.69 - 284.22)	0.30	158 (134.32 - 184.65)	752.69 (727.68 - 778.39)	0.40
		178 (152.81 - 206.16)		0.45	226 (197.49 - 257.47)		0.57
COVISHIELD/ AstraZeneca	2,752,733	7 (2.81 - 14.42)	19.94 (19.26 - 20.57)	0.25	10 (4.80 - 18.39)	59.12 (57.18 - 61.09)	0.36
		7 (2.81 - 14.42)		0.25	11 (5.49 - 19.68)		0.25

¹Only cases that had a vaccine trade name were included in the observed counts. Reports were excluded if time to onset was greater than 7 days for a time at risk of 7 days and 21 days for a time at risk of 21 days.

²Broad definition includes the following ICD-10-CA codes: I09.0 (Rheumatic myocarditis), I30.x (Acute pericarditis), I31.x (Other diseases of the pericardium), I32.x (Pericarditis in disease classified elsewhere), I40.x (Acute myocarditis), I41.x (Myocarditis in disease classified elsewhere), I51.4 (Myocarditis, unspecified).

³Most recent doses administered data as of July 10, 2021.

⁴Observed data as of July 16, 2021 for lower observed case count (CAEFISS and CVD cases); observed data as of July 16, 2021 for higher observed case count (CAEFISS, CVD, and cases submitted via email by provinces/territories). In an effort to obtain a close-to-real time view of this issue, provincial and territorial vaccine safety officials were asked to email PHAC information on all active cases of myocarditis/pericarditis. In response, several provinces submitted their current myocarditis/pericarditis case counts to PHAC (n=135 additional cases). Please note that not all of the cases have been entered or medically reviewed by PHAC. Some cases may be duplicates.

⁵MaxSPRT methods were ran on cells where the observed count was found to be significantly great than the expected count at the 5% significance level in order to account for the sequential nature of the analysis. Cells in red indicate that the observed count is significantly greater than the expected count and this difference holds at the 1% significance level using maxSPRT. Cells in orange indicate that the observed count is significantly greater than the expected count and this difference holds at the 5% significance level using maxSPRT. Cells in green indicate that the observed count is significantly greater than the expected count but this difference dose not hold using maxSPRT.

*95% confidence intervals for observed events were calculated using the Poisson exact method.

**95% confidence intervals for the number of expected events were calculated using the Poisson exact confidence intervals around the age and sex specific background rates.

Please note: Parts of this material are based on data and information compiled and provided by CIHI. However, the analyses, conclusions, opinions and statements expressed herein are those of the author, and not necessarily those of CIHI.

Source: Discharge Abstract Database and National Ambulatory Care Reporting System, Canadian Institute for Health Information, Fiscal years 2014-2019; Canadian COVID-19 Vaccination Coverage Surveillance System (CCVCSS); CAEFISS database; Canada Vigilance database.

Table 4a: Myocarditis/pericarditis reports to CAEFISS and CVD, in addition to emailed reports, following **dose 1 Pfizer/BioNTech** COVID-19 vaccination, Observed vs. Expected^{1,2} by vaccine type, age groups and sex, using a time at risk of **7 and 21 days**.

Age groups	Males				Females			
	Doses admin ³	Observed ⁴ (CI)*	Expected (CI)**	Rate (per 100,000 doses admin)	Doses admin ³	Observed ⁴ (CI)*	Expected (CI)**	Rate (per 100,000 doses admin)
Time at risk = 7 days								
12 to 17	835,069	6 (2.20 - 13.06)	2.29 (2.12 - 2.46)	0.72	823,694	2 (0.24 - 7.22)	0.85 (0.74 - 0.96)	0.24
		6 (2.20 - 13.06)		0.72		3 (0.62 - 8.77)		0.36
18 to 29	1,460,735	4 (1.09 - 10.24)	10.52 (10.21 - 10.83)	0.27	1,566,596	2 (0.24 - 7.22)	4.16 (3.96 - 4.38)	0.13
		7 (2.81 - 14.42)		0.48		4 (1.09 - 10.24)		0.26
30 to 39	1,344,566	4 (1.09 - 10.24)	9.12 (8.82 - 9.44)	0.30	1,475,683	3 (0.62 - 8.77)	4.37 (4.15 - 4.59)	0.20
		6 (2.20 - 13.06)		0.45		3 (0.62 - 8.77)		0.20
Time at risk = 21 days								
12 to 17	835,069	6 (2.20 - 13.06)	6.65 (6.16 - 7.17)	0.72	823,694	2 (0.24 - 7.22)	2.47 (2.17 - 2.79)	0.24
		7 (2.81 - 14.42)		0.84		3 (0.62 - 8.77)		0.36
18 to 29	1,460,735	7 (2.81 - 14.42)		0.48	1,566,596	3 (0.62 - 8.77)		0.19

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		11 (5.49-19.68)	31.1 (30.19 - 32.02)	0.75		5 (1.62 - 11.67)	12.35 (11.74 - 12.98)	0.32
30 to 39	1,344,566	5 (1.62 - 11.67)	27.1 (26.2 - 28.02)	0.37	1,475,683	4 (1.09 - 10.24)	12.98 (12.33 - 13.65)	0.27
		7 (2.81 - 14.42)		0.52		4 (1.09 - 10.24)		0.27

Table 4b: Myocarditis/pericarditis reports to CAEFISS and CVD, in addition to emailed reports, following **dose 2 Pfizer/BioNTech** COVID-19 vaccination, Observed vs. Expected^{1,2} by vaccine type, age groups and sex, using a time at risk of **7 and 21 days**.

Age groups	Males				Females			
	Doses admin ³	Observed ⁴ (CI)*	Expected (CI)**	Rate (per 100,000 doses admin)	Doses admin ³	Observed ⁴ (CI)*	Expected (CI)**	Rate (per 100,000 doses admin)
Time at risk = 7 days								
12 to 17	191,422	1 (0.03 - 5.57)	0.49 (0.46 - 0.53)	0.52	199,239	1 (0.03 - 5.57)	0.19 (0.17 - 0.22)	0.50
		5 (1.62 - 11.67)		2.61		1 (0.03 - 5.57)		0.50
18 to 29	424,991	5 (1.62 - 11.67)	2.94 (2.85 - 3.02)	1.18	612,510	1 (0.03 - 5.57)	1.58 (1.5 - 1.66)	0.16
		9 (4.12 - 17.08)		2.12		2 (0.24 - 7.22)		0.33
30 to 39	500,685	2 (0.24 - 7.22)	3.27 (3.16 - 3.38)	0.40	677,953	4 (1.09 - 10.24)	1.95 (1.85 - 2.05)	0.59
		2 (0.24 - 7.22)		0.40		4 (1.09 - 10.24)		0.59
Time at risk = 21 days								
12 to 17	191,422	1 (0.03 - 5.57)	0.85 (0.79 - 0.92)	0.52	199,239	1 (0.03 - 5.57)	0.34 (0.3 - 0.38)	0.50
		5 (1.62 - 11.67)		2.61		1 (0.03 - 5.57)		0.50
18 to 29	424,991	5 (1.62 - 11.67)	6.25 (6.07 - 6.44)	1.18	612,510	1 (0.03 - 5.57)	3.7 (3.52 - 3.89)	0.16
		9 (4.12 - 17.08)		2.12		2 (0.24 - 7.22)		0.33

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30 to 39	500,685	3 (0.62 - 8.77)	7.17 (6.93 - 7.42)	0.60	677,953	5 (1.62 - 11.67)	4.63 (4.4 - 4.87)	0.74
		3 (0.62 - 8.77)		0.60		6 (2.20 - 13.06)		0.89

Table 4c: Myocarditis/pericarditis reports to CAEFISS and CVD, in addition to emailed reports, following any dose of **Pfizer/BioNTech** COVID-19 vaccination, by vaccine type, age groups and sex, using a time at risk of 7 and 21 days.

Age groups	Males				Females			
	Doses admin ³	Observed ⁴ (CI)*	Expected (CI)**	Rate (per 100,000 doses admin)	Doses admin ³	Observed ⁴ (CI)*	Expected (CI)**	Rate (per 100,000 doses admin)
Time at risk = 7 days								
12 to 17	1,024,952	8 (3.45 - 15.76)	2.8 (2.59 - 3.01)	0.78	1,021,145	3 (0.62 - 8.77)	1.04 (0.92 - 1.18)	0.29
		12 (6.20 - 20.96)		1.17		4 (1.09 - 10.24)		0.39
18 to 29	1,882,657	11 (5.49 - 19.68)	13.48 (13.09 - 13.88)	0.58	2,175,842	4 (1.09 - 10.24)	5.75 (5.47 - 6.04)	0.18
		18 (10.67 - 28.45)		0.96		7 (2.81 - 14.42)		0.32
30 to 39	1,841,463	8 (3.45 - 15.76)	12.42 (12.01 - 12.85)	0.43	2,150,273	7 (2.81 - 14.42)	6.33 (6.01 - 6.65)	0.33
		10 (4.80 - 18.39)		0.54		7 (2.81 - 14.42)		0.33
Time at risk = 21 days								
12 to 17	1,024,952	8 (3.45 - 15.76)	7.81 (7.24 - 8.41)	0.78	1,021,145	3 (0.62 - 8.77)	2.92 (2.56 - 3.3)	0.29
		13 (6.92 - 22.23)		1.27		4 (1.09 - 10.24)		0.39
18 to 29	1,882,657	15 (8.40 - 24.74)	37.65 (36.56 - 38.77)	0.80	2,175,842	5 (1.62 - 11.67)	16.06 (15.27 - 16.88)	0.23
		23 (14.58 - 34.51)		0.96		8 (3.45 - 15.76)		0.37

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30 to 39	1,841,463	10 (4.80 - 18.39)	34.7 (33.55 - 35.88)	0.54	2,150,273	9 (4.12 - 17.08)	17.67 (16.79 - 18.59)	0.42
		12 (6.20 - 20.96)		0.65		10 (4.80 - 18.39)		0.47

Table 5a: Myocarditis/pericarditis reports to CAEFISS and CVD, in addition to emailed reports, following **dose 1 Moderna** COVID-19 vaccination, Observed vs. Expected^{1,2} by vaccine type, age groups and sex, using a time at risk of **7 and 21 days**.

Age groups	Males				Females			
	Doses admin ³	Observed ⁴ (CI)*	Expected (CI)**	Rate (per 100,000 doses admin)	Doses admin ³	Observed ⁴ (CI)*	Expected (CI)**	Rate (per 100,000 doses admin)
Time at risk = 7 days								
12 to 17	3,119	0 (0.00 - 3.00)	0.01 (0.01 - 0.01)	0	3,396	0 (0.00 - 3.00)	0 (0 - 0)	0
		0 (0.00 - 3.00)		0		0 (0.00 - 3.00)		0
18 to 29	523,421	4 (1.09 - 10.24)	3.74 (3.63 - 3.85)	0.76	486,181	1 (0.03 - 5.57)	1.28 (1.22 - 1.35)	0.21
		4 (1.09 - 10.24)		0.76		1 (0.03 - 5.57)		0.21
30 to 39	476,088	2 (0.24 - 7.22)	3.21 (3.11 - 3.32)	0.42	450,999	0 (0.00 - 3.00)	1.33 (1.26 - 1.4)	0
		2 (0.24 - 7.22)		0.42		0 (0.00 - 3.00)		0
Time at risk = 21 days								
12 to 17	3,119	0 (0.00 - 3.00)	0.02 (0.02 - 0.03)	0	3,396	0 (0.00 - 3.00)	0.01 (0.01 - 0.01)	0
		0 (0.00 - 3.00)		0		0 (0.00 - 3.00)		0
18 to 29	523,421	5 (1.62- 11.67)	10.43 (10.13 - 10.74)	0.96	486,181	2 (0.24 - 7.22)	3.63 (3.45 - 3.81)	0.41
		6 (2.20- 13.06)		1.15		3 (0.62 - 8.77)		0.62

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30 to 39	476,088	3 (0.62 - 8.77)	9.12 (8.82 - 9.43)	0.63	450,999	0 (0.00 - 3.00)	3.8 (3.61 - 3.99)	0
		3 (0.62 - 8.77)		0.63		0 (0.00 - 3.00)		0

Table 5b: Myocarditis/pericarditis reports to CAEFISS and CVD, in addition to emailed reports, following **dose 2 Moderna** COVID-19 vaccination, Observed vs. Expected^{1,2} by vaccine type, age groups and sex, using a time at risk of **7 and 21 days**.

Age groups	Males				Females			
	Doses admin ³	Observed ⁴ (CI)*	Expected (CI)**	Rate (per 100,000 doses admin)	Doses admin ³	Observed ⁴ (CI)*	Expected (CI)**	Rate (per 100,000 doses admin)
Time at risk = 7 days								
12 to 17	1,117	0 (0.00 - 3.00)	0 (0 - 0)	0	1,495	0 (0.00 - 3.00)	0 (0 - 0)	0
		0 (0.00 - 3.00)		0		0 (0.00 - 3.00)		0
18 to 29	345,458	15 (8.40 - 24.74)	2.37 (2.3 - 2.44)	4.34	364,703	3 (0.62 - 8.77)	0.93 (0.88 - 0.97)	0.82
		36 (25.21 - 49.84)		10.42		4 (1.09 - 10.24)		1.10
30 to 39	371,667	2 (0.24 - 7.22)	2.41 (2.33 - 2.49)	0.54	370,541	3 (0.62 - 8.77)	1.05 (1 - 1.11)	0.81
		6 (2.20 - 13.06)		1.61		5 (1.62 - 11.67)		1.35
Time at risk = 21 days								
12 to 17	1,117	0 (0.00 - 3.00)	0.01 (0.01 - 0.01)	0	1,495	0 (0.00 - 3.00)	0 (0 - 0)	0
		0 (0.00 - 3.00)		0		0 (0.00 - 3.00)		0
18 to 29	345,458	15 (8.40 - 24.74)	4.76 (4.62 - 4.9)	4.34	364,703	3 (0.62 - 8.77)	1.93 (1.84 - 2.03)	0.82
		36 (25.21 - 49.84)		10.42		4 (1.09 - 10.24)		1.10

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30 to 39	371,667	2 (0.24 - 7.22)	4.99 (4.82 - 5.16)	0.54	370,541	3 (0.62 - 8.77)	2.26 (2.14 - 2.37)	0.81
		6 (2.20 - 13.06)		1.61		5 (1.62 - 11.67)		1.35

Table 5c: Myocarditis/pericarditis reports to CAEFISS and CVD, in addition to emailed reports, following any dose of **Moderna** COVID-19 vaccination, by vaccine type, age groups and sex, using a time at risk of 7 and 21 days.

Age groups	Males				Females			
	Doses admin ³	Observed ⁴ (CI)*	Expected (CI)**	Rate (per 100,000 doses admin)	Doses admin ³	Observed ⁴ (CI)*	Expected (CI)**	Rate (per 100,000 doses admin)
Time at risk = 7 days								
12 to 17	4,236	0 (0.00 - 3.00)	0.01 (0.01 - 0.01)	0	4,891	0 (0.00 - 3.00)	0.01 (0 - 0.01)	0
		0 (0.00 - 3.00)		0		0 (0.00 - 3.00)		0
18 to 29	868,879	21 (13.00 - 32.10)	6.24 (6.06 - 6.42)	2.42	850,884	5 (1.62 - 11.67)	2.26 (2.14 - 2.37)	0.59
		42 (30.27 - 56.77)		4.83		6 (2.20 - 13.06)		0.71
30 to 39	847,755	5 (1.62 - 11.67)	5.74 (5.55 - 5.93)	0.59	821,540	3 (0.62 - 8.77)	2.42 (2.3 - 2.55)	0.37
		9 (4.12 - 17.08)		1.06		5 (1.62 - 11.67)		0.61
Time at risk = 21 days								
12 to 17	4,236	0 (0.00 - 3.00)	0.03 (0.03 - 0.03)	0	4,891	0 (0.00 - 3.00)	0.01 (0.01 - 0.01)	0
		0 (0.00 - 3.00)		0		0 (0.00 - 3.00)		0
18 to 29	868,879	22 (13.79 - 33.31)	16.11 (15.64 - 16.59)	2.53	850,884	6 (2.20 - 13.06)	5.82 (5.54 - 6.12)	0.71
		44 (31.97 - 59.07)		4.83		8 (3.45 - 15.76)		0.94

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30 to 39	847,755	6 (2.20 - 13.06)	14.82 (14.32 - 15.32)	0.71	821,540	3 (0.62 - 8.77)	6.26 (5.95 - 6.59)	0.37
		10 (4.80 - 18.39)		1.18		5 (1.62 - 11.67)		0.61

Table 6a: Myocarditis/pericarditis reports to CAEFISS and CVD, in addition to emailed reports, following **dose 1 mRNA COVID-19** vaccination, Observed vs. Expected^{1,2} by vaccine type, age groups and sex, using a time at risk of **7 and 21 days**.

Age groups	Males				Females			
	Doses admin ³	Observed ⁴ (CI)*	Expected (CI)**	Rate (per 100,000 doses admin)	Doses admin ³	Observed ⁴ (CI)*	Expected (CI)**	Rate (per 100,000 doses admin)
Time at risk = 7 days								
12 to 17	838,188	6 (2.20 - 13.06)	2.29 (2.13 - 2.47)	0.72	827,090	2 (0.24 - 7.22)	0.85 (0.75 - 0.96)	0.24
		6 (2.20 - 13.06)		0.72		3 (0.62 - 8.77)		0.36
18 to 29	1,984,156	8 (3.45 - 15.76)	14.25 (13.84 - 14.68)	0.40	2,052,777	3 (0.62 - 8.77)	5.45 (5.18 - 5.73)	0.15
		11 (5.49 - 19.68)		0.55		5 (1.62 - 11.67)		0.24
30 to 39	1,820,654	6 (2.20 - 13.06)	12.34 (11.93 - 12.76)	0.33	1,926,682	3 (0.62 - 8.77)	5.7 (5.41 - 5.99)	0.16
		8 (3.45 - 15.76)		0.44		3 (0.62 - 8.77)		0.16
Time at risk = 21 days								
12 to 17	838,188	6 (2.20 - 13.06)	6.67 (6.19 - 7.19)	0.72	827,090	2 (0.24 - 7.22)	2.48 (2.18 - 2.8)	0.24
		7 (2.81 - 14.42)		0.84		3 (0.62 - 8.77)		0.36
18 to 29	1,984,156	12 (6.20 - 20.96)	41.53 (40.32 - 42.76)	0.60	2,052,777	5 (1.62 - 11.67)	15.97 (15.19 - 16.79)	0.24
		17 (9.90 - 27.22)		0.86		8 (3.45 - 15.76)		0.39

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30 to 39	1,820,654	8 (3.45 - 15.76)	36.21 (35.01 - 37.45)	0.44	1,926,682	4 (1.09 - 10.24)	16.78 (15.94 - 17.65)	0.21
		10 (4.80 - 18.39)		0.55		4 (1.09 - 10.24)		0.21

Table 6b: Myocarditis/pericarditis reports to CAEFISS and CVD, in addition to emailed reports, following **dose 2 mRNA COVID-19** vaccination, Observed vs. Expected^{1,2} by vaccine type, age groups and sex, using a time at risk of **7 and 21 days**.

Age groups	Males				Females			
	A Doses admin ³	Observed ⁴ (CI)*	Expected (CI)**	Rate (per 100,000 doses admin)	Doses admin ³	Observed ⁴ (CI)*	Expected (CI)**	Rate (per 100,000 doses admin)
Time at risk = 7 days								
12 to 17	192,539	1 (0.03 - 5.57)	0.49 (0.46 - 0.53)	0.52	200,734	1 (0.03 - 5.57)	0.19 (0.17 - 0.22)	0.50
		5 (1.62 - 11.67)		2.60		1 (0.03 - 5.57)		0.50
18 to 29	770,449	20 (12.22 - 30.89)	5.3 (5.15 - 5.46)	2.60	977,213	4 (1.09 - 10.24)	2.51 (2.38 - 2.64)	0.41
		45 (32.82 - 60.21)		5.84		6 (2.20 - 13.06)		0.61
30 to 39	872,352	4 (1.09 - 10.24)	5.68 (5.49 - 5.87)	0.46	1,048,494	7 (2.81 - 14.42)	3 (2.85 - 3.16)	0.67
		8 (3.45 - 15.76)		0.92		9 (4.12 - 17.08)		0.86
Time at risk = 21 days								
12 to 17	192,539	1 (0.03 - 5.57)	0.86 (0.8 - 0.93)	0.52	200,734	1 (0.03 - 5.57)	0.34 (0.3 - 0.39)	0.50
		5 (1.62 - 11.67)		2.60		1 (0.03 - 5.57)		0.50
18 to 29	770,449	20 (12.22 - 30.89)	11.01 (10.69 - 11.34)	2.60	977,213	4 (1.09 - 10.24)	5.63 (5.35 - 5.92)	0.41
		45 (32.82 - 60.21)		5.84		6 (2.20 - 13.06)		0.61

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30 to 39	872,352	5 (1.62 - 11.67)	12.16 (11.76 - 12.57)	0.57	1,048,494	8 (3.45 - 15.76)	6.89 (6.55 - 7.25)	0.76
		9 (4.12 - 17.08)		1.03		11 (5.49 - 19.68)		1.05

Table 6c: Myocarditis/pericarditis reports to CAEFISS and CVD, in addition to emailed reports, following any dose of mRNA COVID-19 vaccination, by vaccine type, age groups and sex, using a time at risk of 7 and 21 days.

Age groups	Males				Females			
	Doses admin ³	Observed ⁴ (CI)*	Expected (CI)**	Rate (per 100,000 doses admin)	Doses admin ³	Observed ⁴ (CI)*	Expected (CI)**	Rate (per 100,000 doses admin)
Time at risk = 7 days								
12 to 17	1,030,727	8 (3.45 - 15.76)	2.81 (2.6 - 3.03)	0.78	1,027,824	3 (0.62 - 8.77)	1.05 (0.92 - 1.19)	0.29
		12 (6.20 - 20.96)		1.16		4 (1.09 - 10.24)		0.39
18 to 29	2,061,205	32 (21.89 - 45.17)	19.71 (19.14 - 20.3)	1.55	3,029,990	9 (4.12 - 17.08)	8 (7.61 - 8.41)	0.30
		60 (45.79 - 77.23)		2.91		13 (6.92 - 22.23)		0.43
30 to 39	2,693,006	13 (6.92 - 22.23)	18.16 (17.55 - 18.77)	0.48	2,975,176	10 (4.80 - 18.39)	8.75 (8.31 - 9.2)	0.34
		19 (11.44 - 29.67)		0.71		12 (6.20 - 20.96)		0.40
Time at risk = 21 days								
12 to 17	1,030,727	8 (3.45 - 15.76)	7.7 (7.13 - 8.29)	0.78	1,027,824	3 (0.62 - 8.77)	2.88 (2.53 - 3.26)	0.29
		13 (6.92 - 22.23)		1.26		4 (1.09 - 10.24)		0.39
18 to 29	2,061,205	37 (26.05 - 51.00)	53.99 (52.42 - 55.59)	1.80	3,029,990	11 (5.49 - 19.68)	21.92 (20.84 - 23.04)	0.36
		67 (51.92 - 85.09)		2.91		16 (9.15 - 25.98)		0.53

30 to 39	2,693,006	16 (9.15 - 25.98)	49.72 (48.07 - 51.41)	0.59	2,975,176	12 (6.20 - 20.96)	23.96 (22.77 - 25.2)	0.40
		22 (13.79 - 33.31)		0.82		15 (8.40 - 24.74)		0.50

This footnote applies to Table 4a and to Table 6c.

¹Only cases with vaccine trade name, age and sex were included in the observed counts. Reports were excluded if time to onset was greater than 7 days for a time at risk of 7 days and 21 days for a time at risk of 21 days.

²Based on broad observed/expected definition. Broad definition includes the following ICD-10-CA codes: *I01.0 (Acute rheumatic pericarditis), I01.2 (Acute rheumatic myocarditis), I09.0 (Rheumatic myocarditis), I09.2 (Chronic rheumatic pericarditis), I30.x (Acute pericarditis), I31.x (Other diseases of the pericardium), I32.x (Pericarditis in disease classified elsewhere), I40.x (Acute myocarditis), I41.x (Myocarditis in disease classified elsewhere), I51.4 (Myocarditis, unspecified).*

³Most recent doses administered data as of July 10, 2021. For the dose specific analyses, doses administered from QC as of July 11, 2021 were used. The doses administered used for the dose-specific analyses may be underreported as the following doses were excluded: 1. Doses with missing age and/or sex. 2. Doses administered by the CAF or CSC.

⁴Observed data as of July 16, 2021 for lower observed case count (CAEFISS and CVD cases); observed data as of July 16, 2021 for higher observed case count (CAEFISS, CVD, and cases submitted via email by provinces/territories). In an effort to obtain a close-to-real time view of this issue, provincial and territorial vaccine safety officials were asked to email PHAC information on all active cases of myocarditis/pericarditis. In response, several provinces submitted their current myocarditis/pericarditis case counts to PHAC (n=135 additional cases). Please note that not all of the cases have been entered or medically reviewed by PHAC. Some cases may be duplicates.

⁵MaxSPRT methods were ran on cells where the observed count was found to be significantly great than the expected count at the 5% significance level in order to account for the sequential nature of the analysis. Cells in red indicate that the observed count is significantly greater than the expected count and this difference holds at the 1% significance level using maxSPRT. Cells in orange indicate that the observed count is significantly greater than the expected count and this difference holds at the 5% significance level using maxSPRT. Cells in green indicate that the observed count is significantly greater than the expected count but this difference does not hold using maxSPRT.

*95% confidence intervals for observed events were calculated using the Poisson exact method.

**95% confidence intervals for the number of expected events were calculated using the Poisson exact confidence intervals around the age and sex specific background rates.

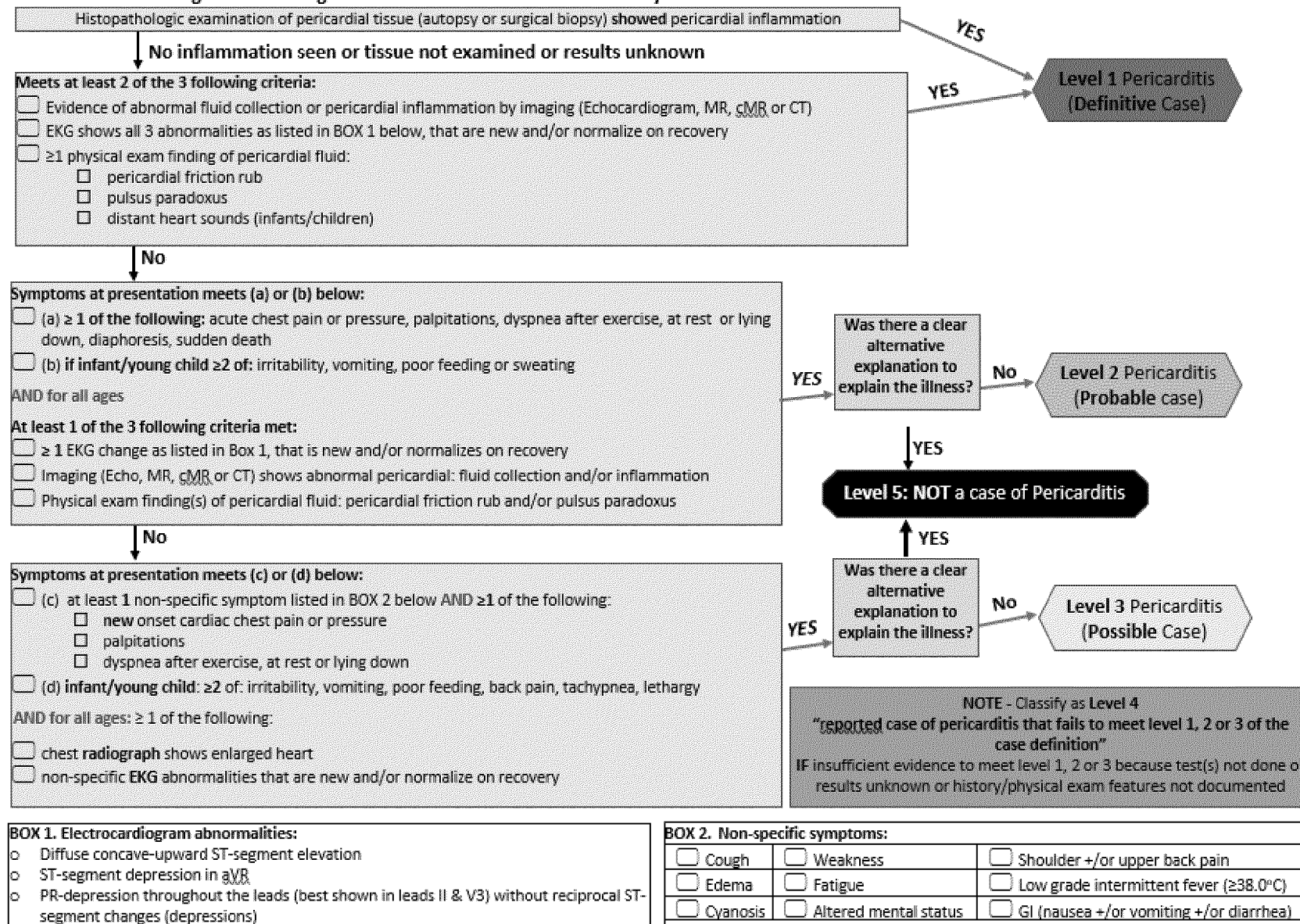
Please note: Parts of this material are based on data and information compiled and provided by CIHI. However, the analyses, conclusions, opinions and statements expressed herein are those of the author, and not necessarily those of CIHI.

Source: Discharge Abstract Database and National Ambulatory Care Reporting System, Canadian Institute for Health Information, Fiscal years 2014-2019; Canadian COVID-19 Vaccination Coverage Surveillance System (CCVCSS); INSPQ; CAEFISS database, Canada Vigilance database.

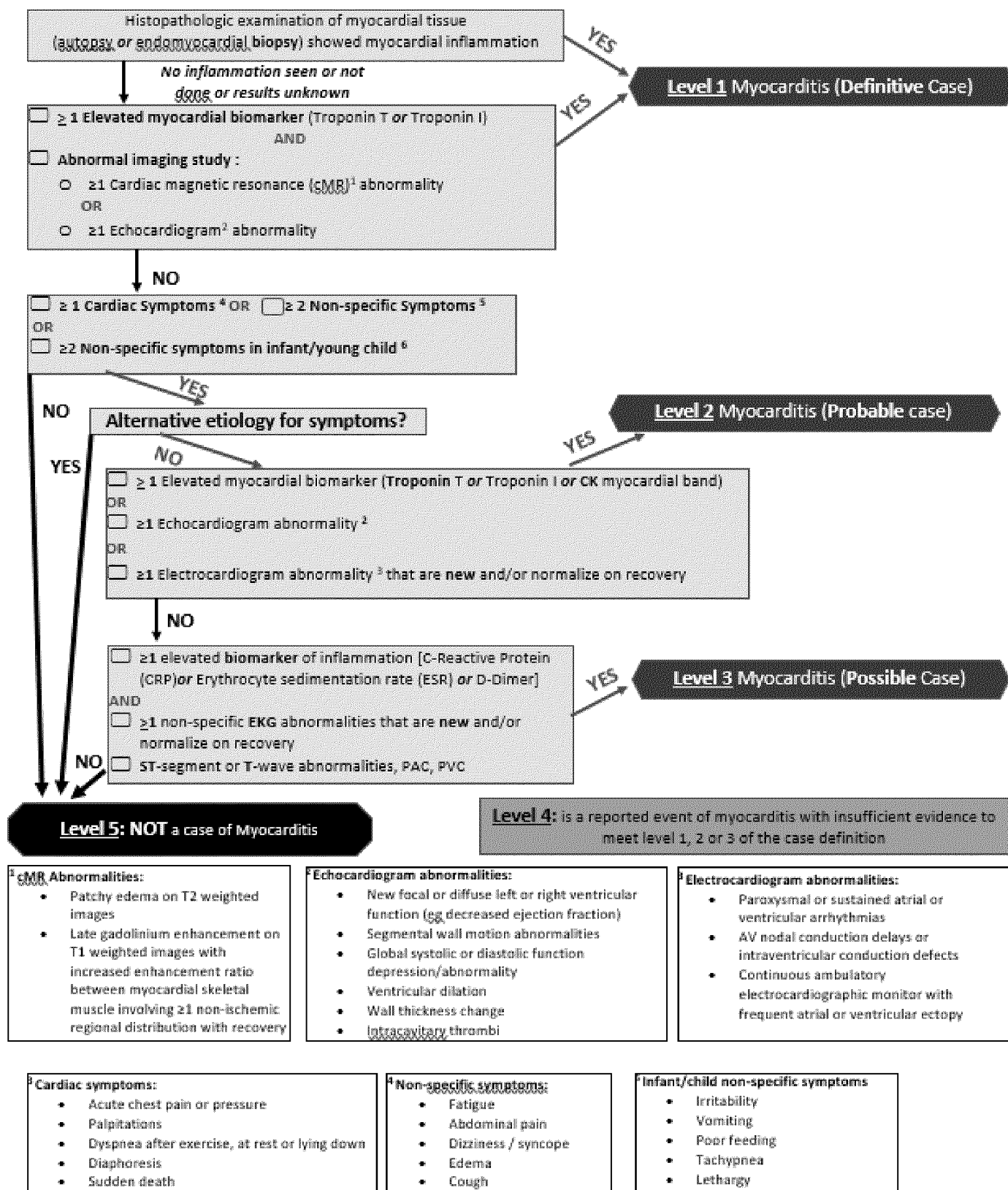
Appendix B

Brighton Collaboration Criteria for Myocarditis and Pericarditis:

PERICARDITIS: Algorithm for Brighton Case Definition Levels of Certainty



Myocarditis: Algorithm for Brighton Case Definition Levels of Certainty



Marketed Health Products Directorate
Direction des produits de santé commercialisés

PERIODIC BENEFIT-RISK EVALUATION REPORT (PBRER) REVIEW
COMPREHENSIVE

PFIZER-BIONTECH COVID-19 VACCINE (BNT162B2, TOZINAMERAN)

SUMMARY MONTHLY SAFETY REPORT 6
30 APRIL 2021 TO 31 MAY 2021

CONTROL # 253419

(Including the MAH's Response to MHPD Requests under control number 253419)

Position Title: Director / Directeur(ice)
Bureau: Bureau of Biologics, Radiopharmaceuticals and Self-Care Products/ Bureau des produits biologiques, radiopharmaceutiques et auto-administratifs
Date: 07 July 2021
Signature: This document has been signed electronically using the Health Canada docuBridge system. / Ce document a été signé électroniquement à l'aide du système docuBridge de Santé Canada
Security – Classification – de sécurité: Protected B when completed / protégé B une fois terminé

EXECUTIVE SUMMARY

This Summary Monthly Safety Report 6 for the Pfizer-BioNTech COVID-19 Vaccine (BNT162B2, tozinameran) covers the period from 30 April 2021 to 31 May 2021.

Pfizer-BioNTech COVID-19 Vaccine (BNT162B2, tozinameran) is indicated for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS- CoV-2) in individuals 12 years of age and older.

The Pfizer-BioNTech COVID-19 Vaccine (BNT162B2, tozinameran) received marketing authorization in Canada under the *Interim Order Respecting the Importation, Sale and Advertising of Drugs for Use in Relation to COVID-19* (control no. 244906; 09 December 2020). The interim authorization of the Pfizer-BioNTech COVID-19 Vaccine is subject to Terms and Conditions that need to be met by the MAH. The Pfizer-BioNTech COVID-19 Vaccine has received temporary authorisation for emergency supply in 35 countries and conditional marketing authorisation approval in 43 countries globally.

The scope of this review is to assess the Summary Monthly Safety Report (SMSR) #6 for Pfizer-BioNTech COVID-19 Vaccine and determine whether the Terms and Conditions relevant to adverse events reporting are met by the MAH and to follow-up on issues that have been identified by the MHPD during the previous reporting interval.

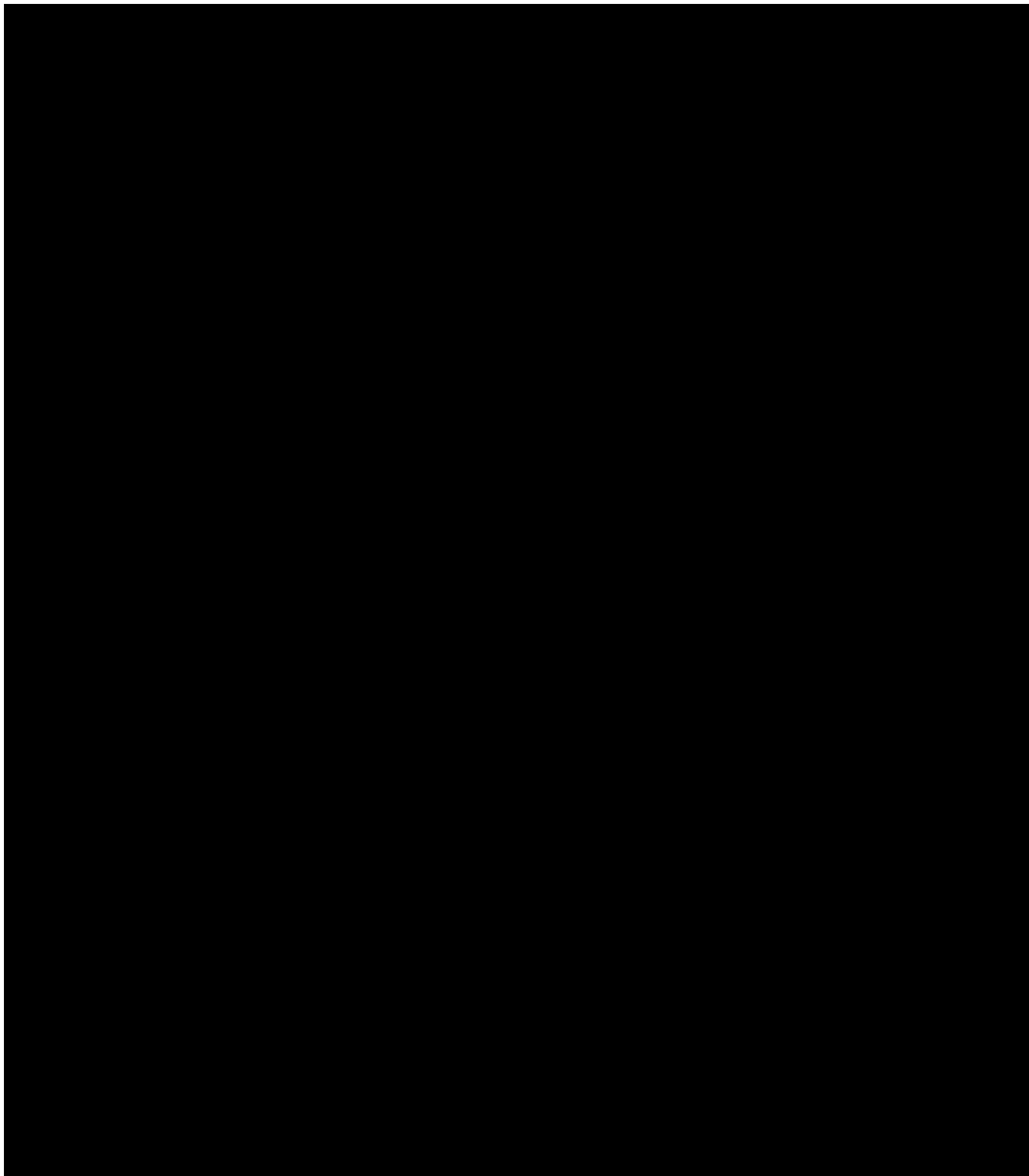
It was estimated that approximately 220,976,340 doses of the Pfizer-BioNTech COVID-19 Vaccine were shipped worldwide during the current reporting interval from 30 April 2021 to 31 May 2021. Of these, 10,452,780 doses were shipped to Canada. Of these, 8,884,863 were administered in Canada in the current interval.

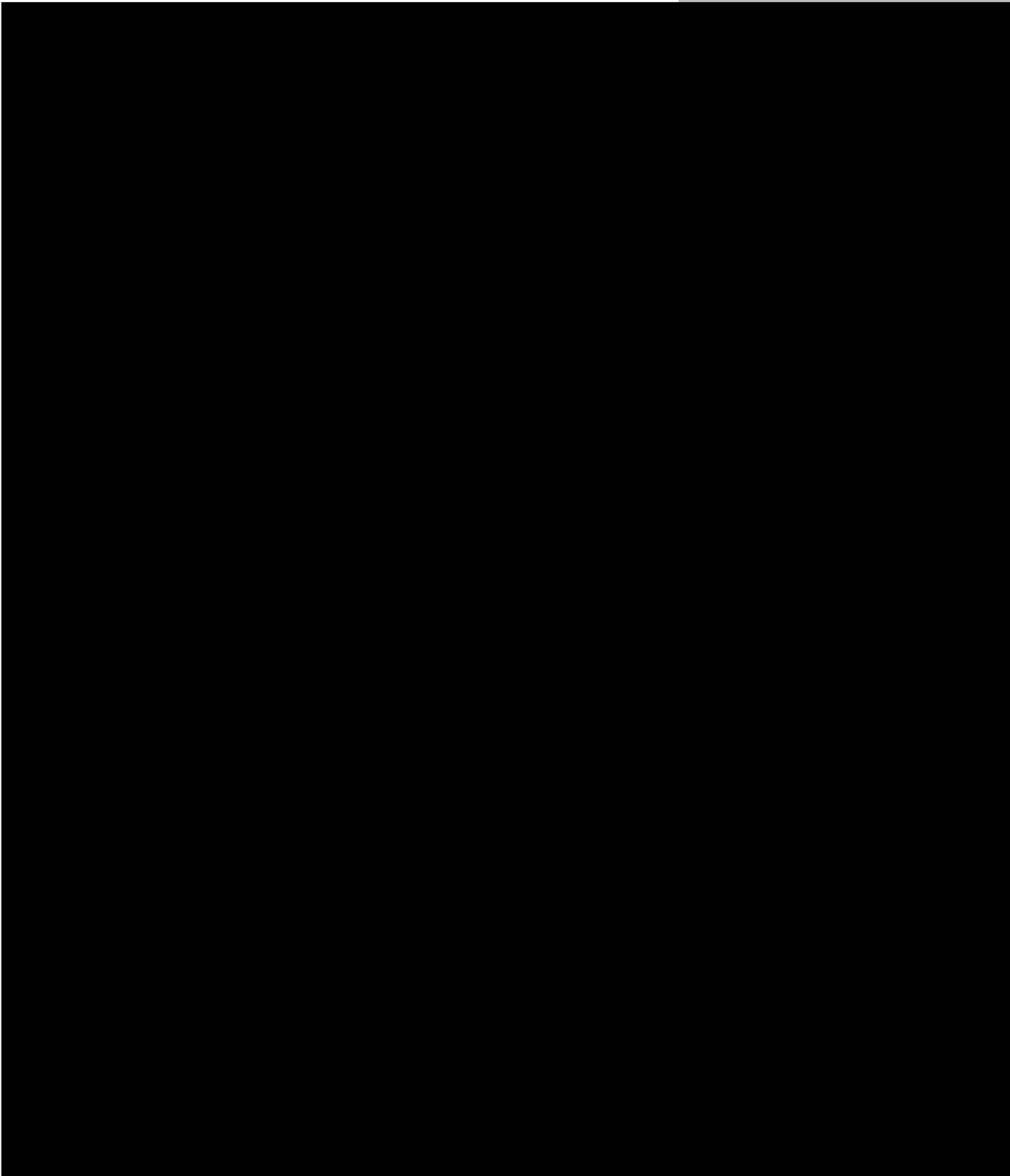
A total of 47,174 cases with 174,446 adverse events were reported during this interval. Of the 47,174 cases

- 43 % of the reported cases were assessed as serious (20,288), 57% of the cases (26,885) were assessed as nonserious
- The majority of cases were from the United Kingdom (10,047) and the United States (8,975). Four hundred and twenty-three cases (423) were from Canada. One hundred and ninety (190) cases were in the previous interval period.
- Women represented the majority of the reported cases with 32,751 cases and men represented 11,506 cases (unknown data in 2,917 cases).
- The median age was 49.0 years old, with approximately a third of the cases 14,682 cases between the ages of 31 and 50 years old. Corresponding figures for age \leq 17 years old and age \geq 65 years old were 327 and 10,167, respectively (unknown age in 7,391 cases).
- Nine hundred and seventy-one (971) cases had a fatal outcome.

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¹ <https://www.gov.uk/government/publications/regulatory-approval-of-pfizer-biontech-vaccine-for-covid-19/information-for-healthcare-professionals-on-pfizerbiontech-covid-19-vaccine>

² <https://www.fda.gov/media/144413/download>

³ https://www.ema.europa.eu/en/documents/product-information/comirnaty-epar-product-information_en.pdf

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1 INTRODUCTION

Control # / SAP #	253419
Canadian Market Authorization Holder (MAH) /Sponsor	Pfizer Canada ULC BioNTech Manufacturing GmbH
Product trade name	Pfizer-BioNTech COVID-19 vaccine
Active ingredient	BNT162B2, tozinameran
International Birth Date (IBD)	19 December 2020 (Switzerland)
Date Notice of Compliance (NOC) issued	09 December 2020
Date of marketing in Canada	14 December 2020
Type of document (PBRER, PSUR, ASR, PADERs, other)	Summary Monthly Safety Report
PBRER # and reporting interval	30 April 2021 to 31 May 2021
Last PBRER reviewed # and reporting interval	01 December 2020 to 31 December 2020 (control no. 248389) 01 January 2021 to 31 January 2021 (control no. 248783) 01 February 2021 to 28 February 2021 (control no. 250059) 01 March 2021 to 31 March 2021 (control no. 251805) 01 April 2021 to 29 April 2021 (control no. 251813)
Last RMP reviewed # and date	European RMP (EU RMP) version 2.0 (control no. 253040) Canadian addendum to the RMP dated May 2021
Date of current Canadian Product Monograph (CPM)	19 May 2021
Other documents submitted with the PBRER	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No Specify:
Foreign review available	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No Specify:
PBRER review type	Comprehensive

1.1 DESCRIPTION OF PRODUCT

BNT162b2 (or tozinameran) is a white to off-white frozen dispersion provided as concentrate for dispersion for injection (sterile concentrate) as multidose vial to be diluted before use. The multidose vial contains 6 doses of 0.3 mL after dilution if low dead-volume syringes and/or needles can be used to extract a 6th dose from a single vial. Each dose contains 30 micrograms of BNT162b2 as well as excipients.

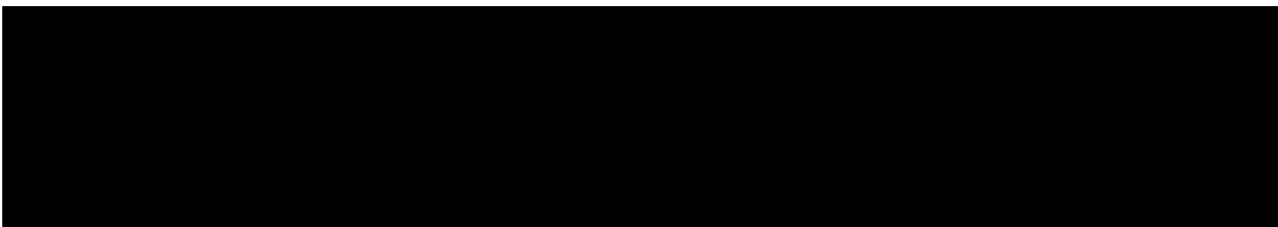
BNT162b2 is single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free *in vitro* transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2.

The nucleoside-modified mRNA is formulated in lipid nanoparticles, which enable delivery of the RNA into host cells to allow expression of the SARS-CoV-2 S antigen. The vaccine elicits both neutralizing antibody and cellular immune responses to the spike (S) antigen, which may contribute to protection against COVID-19.

1.2 PRODUCT USE

1.2a. Authorized indications in Canada

Pfizer-BioNTech COVID-19 Vaccine (COVID-19 mRNA Vaccine) is indicated for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 12 years of age and older.

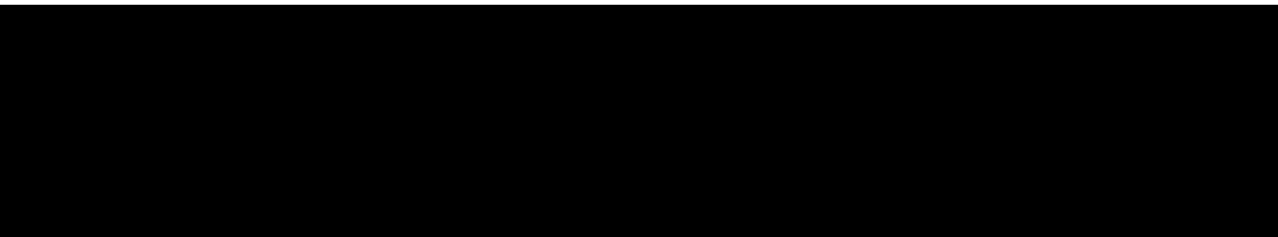


1.2b. Additional indications/uses noted in the PBRER

There is no additional indication noted in the Summary Monthly Safety Report.

1.3 IS THERE A PRE-MARKET SUBMISSION CURRENTLY UNDER REVIEW FOR THIS PRODUCT?

☒ No ☐ Yes



2 TRIGGER AND SCOPE OF THIS REVIEW

On 09 December 2020, the Pfizer-BioNTech COVID-19 Vaccine (BNT162B2, tozinameran) received marketing authorization in Canada under the *Interim Order Respecting the Importation, Sale and Advertising of Drugs for Use in Relation to COVID-19* (control no. 244906). The interim authorization of the Pfizer-BioNTech COVID-19 Vaccine is subject to terms and conditions that need to be met by the MAH. The terms and conditions relevant to adverse events reporting include the following:

Pfizer Canada ULC is required to submit monthly safety reports for the period of the Interim Order authorization, unless otherwise determined by Health Canada. The monthly safety reports should be submitted within 15 days after the last day of a month, beginning after the first full calendar month after authorization. These reports should contain the following:

- Interval and cumulative number of reports (serious and non-serious), overall and by age groups and in special populations (e.g. pregnant women)
- Interval and cumulative number of reports per HLT and SOC
- Number of reports in Canada and Global
- Exposure data, stratified by country, age groups, race and ethnicity
- Changes to reference safety information in the interval
- Ongoing and closed signals in the interval
- List of adverse events of special interest including the Safety Platform for Emergency Vaccines list and RMP safety concerns (including the additional missing information): reports – numbers and relevant cases, including time-to-onset and O/E analyses
- Fatal reports – numbers and relevant cases, including observed/expected analyses
- Vaccination failure / lack of efficacy (including confirmed and suspected cases) and errors – number relevant cases
- Potential interaction with other vaccines/concomitant treatments-number and relevant cases
- Summary outcomes of some of the routine pharmacovigilance activities (as presented in the EU RMP Part III and applied in the Canadian context) should be included for the purpose of rapid signal detection and communication activities. Summary of all ongoing studies can be included in the first six-month scheduled PBRER, unless a safety signal is identified that requires immediate regulatory action.
- Risk/benefit considerations

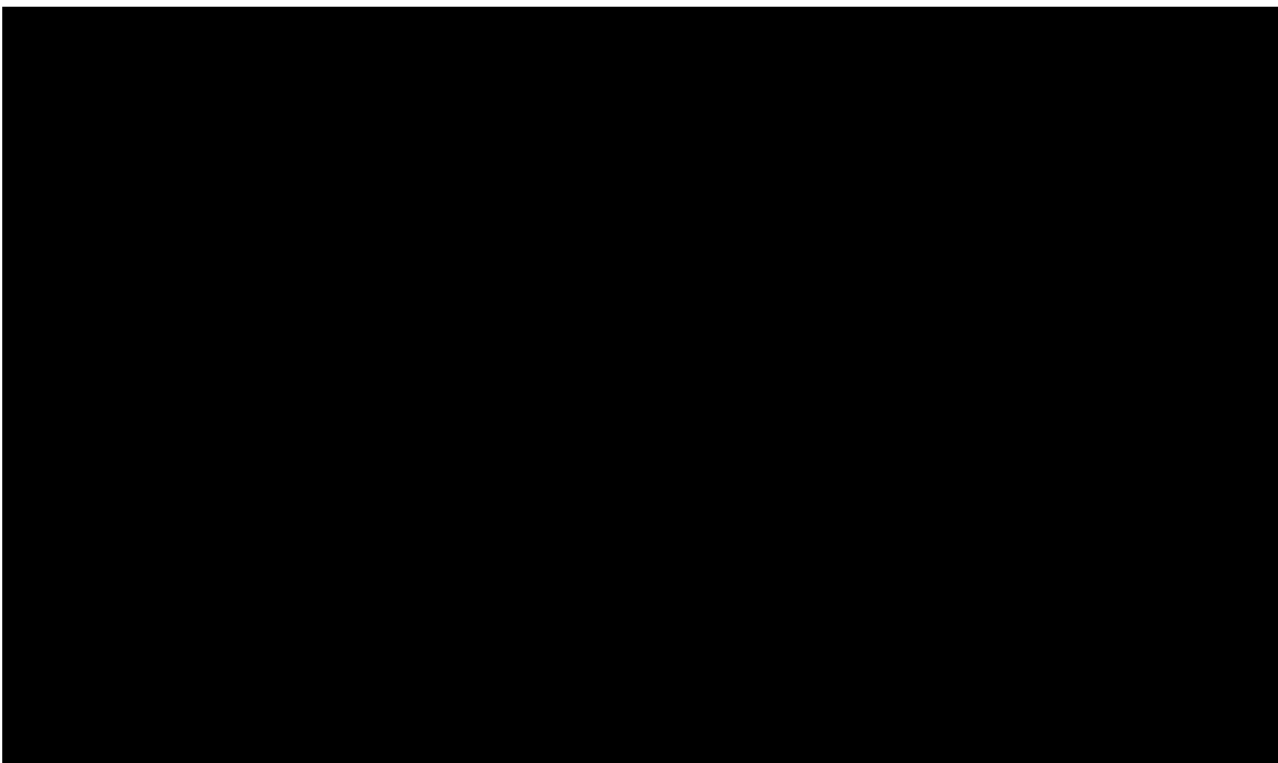
The scope of this review is to assess the current Summary Monthly Safety Report (SMSR) for the Pfizer-BioNTech COVID-19 Vaccine and determine whether the MAH meets the terms and conditions relevant to adverse event reporting (as listed immediately above) and to follow-up on issues that the MHPD identified during the previous reporting interval.

3 ACTIONS TAKEN IN THE REPORTING INTERVAL FOR SAFETY REASONS**3.1 HAVE ACTIONS TAKEN FOR SAFETY REASONS BY THE MAH OR REGULATORY AUTHORITIES BEEN REPORTED?**

☒ Yes ☐ No

Current interval:

No action was reported in the current interval.

Late Breaking information:**4 CHANGES TO THE REFERENCE SAFETY INFORMATION (RSI)**

The RSI for this SMSR is the BNT162b2 Core Data Sheet (CDS) Version 4.0 dated 19 May 2021, in effect at the end of the reporting period.

The previous BNT162B2 CDS Version 3.0 dated 20 April 2021 was also in effect during the reporting period. The MAH updated the CDS version 3.0 on 19 May 2021 to include: Asthenia, Lethargy, Decreased appetite, Hyperhidrosis and Night sweats as adverse drug reactions in Section 4.8 Undesirable effects, and the addition of warning text for Vaccine stress-related responses (including Dizziness, Fainting, Palpitations, Increases in heart rate, Alterations in blood pressure, Feeling short of breath, Tingling sensations, Sweating and/or Anxiety) in Section 4.4 Special warnings and precautions for use.

5 ESTIMATED EXPOSURE AND USE PATTERNS

It is estimated that approximately 639,868,710 doses of the Pfizer-BioNTech COVID-19 Vaccine were shipped worldwide through 31 May 2021, corresponding to approximately 542,013,978 doses administered cumulatively. During the current reporting period (from 30 April 2021 through 31 May 2021) approximately 220,976,340 doses were shipped worldwide corresponding to approximately 188,860,682 doses administered.

In Canada, 20,120,880 doses were shipped cumulatively, corresponding to approximately 17,102,748 doses administered including 8,884,863 doses administered during the reporting period compared to 3,309,696 doses administered in the previous interval.

6 DATA FROM PBRER SUMMARY TABULATIONS AND DATABASE SEARCHES

6.1 ADVERSE REACTION CODING DICTIONARY

The MedDRA version 24.0 was used to code adverse events/reactions during this reporting interval.

6.2 CUMULATIVE SUMMARY TABULATIONS OF SERIOUS ADVERSE EVENTS FROM CLINICAL TRIALS

Adverse events/reactions reported from clinical trials are discussed throughout this report.

6.3 CUMULATIVE AND INTERVAL SUMMARY TABULATIONS OF ADVERSE REACTIONS FROM POST-MARKETING DATA SOURCES

Cumulative number of cases from post-market experience (up to 31 May 2021):

The MAH received 167,956 reports from post-marketing data sources for Pfizer-BioNTech COVID-19 Vaccine through 31 May 2021. Of these, 1142 case reports were from Canada including 423 in the current interval.

Interval number of cases from post market experience (30 April 2021 up to 31 May 2021):

The MAH retrieved 47,174 cases (containing 174,446 events) in the current reporting interval. Of these, 423 cases were from Canada

MedDRA PTs reported in $\geq 2\%$ * Cases in the current interval/cumulative and relevant Canadian labelling

MedDRA SOC MedDRA PT	AEs (AERP%) (interval) N = 47174	AEs (AERP%) N = 167956	CPM Labelling (Y/N)
Blood and lymphatic system disorders			
Lymphadenopathy ^a	1914 (4.06%)	8382 (4.99%)	Y
Cardiac disorders			
Tachycardia	1093 (2.32%)	3596 (2.14%)	Y (partially labelled: fast heartbeat in the context of an allergic reaction, palpitations in the context of myocarditis)
Gastrointestinal disorders			
Nausea ^a	5053 (10.71%)	19303 (11.49%)	Y
Diarrhoea ^a	1786 (3.79%)	6879 (4.10%)	Y
Vomiting ^a	1664 (3.53%)	6253 (3.72%)	Y
General disorders and administration site conditions			
Fatigue ^a	7076 (15.00%)	28432 (16.93%)	Y
Pyrexia ^a	7341 (15.56%)	29507 (17.57%)	Y (fever)
Chills ^a	4990 (10.58%)	20176 (12.01%)	Y
Vaccination site pain ^a	4875 (10.33%)	18829 (11.21%)	Y
Pain ^a	2968 (6.29%)	12683 (7.55%)	Y
Malaise ^a	2968 (6.29%)	12683 (7.55%)	Y (feeling unwell)
Asthenia ^a	3460 (7.33%)	10855 (6.46%)	Y (weakness)
Drug ineffective ^b	1030 (2.18%)	4545 (2.71%)	
Feeling abnormal	4545 (2.71%)	3399 (2.02%)	Y (partial labelling: feeling unwell)
Immune system disorders			
Anaphylactic reaction ^a	758 (2.46%)	1965 (1.79%)	Y
Infections and infestations			
COVID-19 ^b	1898 (4.02%)	7063 (4.21%)	Y
Herpes Zoster	1243 (2.63%)	2234 (1.33%)	N
Musculoskeletal and connective tissue disorders			
Myalgia ^a	5531 (11.72%)	21315 (12.69%)	Y (muscle pain)
Pain in extremity ^a	4103 (8.70%)	15661 (9.32%)	Y
Arthralgia ^a	4282 (9.08%)	16204 (9.65%)	Y (joint pain)
Nervous system disorders			
Headache ^a	11689 (24.78%)	40612 (24.18%)	Y
Dizziness	4039 (8.56%)	13267 (7.90%)	Y

MedDRA SOC MedDRA PT	AEs (AERP%) (interval) N = 47174	AEs (AERP%) N = 167956	CPM Labelling (Y/N)
Paraesthesia	1366 (2.90%)	5337 (3.18%)	N (will be included in RSI)
Hypoaesthesia	1103 (2.34%)	3722 (2.22%)	N
Respiratory, thoracic and mediastinal disorders			
Dyspnoea ^c	1883 (3.90%)	7337 (4.37%)	Y (partially labelled: shortness of breath as part of the case definition of Covid-19)
Cough ^c	1413 (3.00%)	4434 (2.64%)	Y (partially labelled: shortness of breath as part of the case definition of Covid-19)
Oropharyngeal pain	1126 (2.39%)	3408 (2.03%)	N
Skin and subcutaneous tissue disorders			
Rash ^a	1791 (3.80%)	6121 (3.64%)	Y
Pruritus ^a	1949 (4.13%)	3845 (3.51%)	Y
Sensitive skin	1737 (3.68%)	2429 (1.45%)	N
Erythema ^a	1332 (2.82%)	4354 (2.59%)	Y (partially labelled: Redness/local reaction)
Urticaria	1002 (2.12%)	3275 (1.95%)	N
Total number of events	56829	223114	

6.4 CANADIAN ADVERSE REACTION DATA

6.4.1 Was a general search of the Canada Vigilance Database done?

☒ Yes ☐ No

6.4.2 If YES, indicate the Canada Vigilance reference #/date of online search, search strategy, results, and discuss the data

The Marketed Health Products Directorate (MHPD) performs daily Canada Vigilance searches for adverse reaction reports associated with Pfizer-BioNTech COVID-19 Vaccine. Adverse reaction reports are assessed independently by a scientific evaluator and a medical evaluator.

During the reporting interval of 01 April 2021 to 30 April 2021, 326 adverse reactions reports were recorded for the Pfizer-BioNTech. Of these adverse reactions, reports 7 were fatal. All these fatal reports were in patients aged 54, 58, 65 72, 72, 91, 91, 4 males, 1 female. Co-reported PTs include cerebral hemorrhage (2), pulmonary embolism, headache, myocardial infarction (2), cerebrovascular accident, and sudden death .

OTHER SAFETY DATABASES SEARCHES

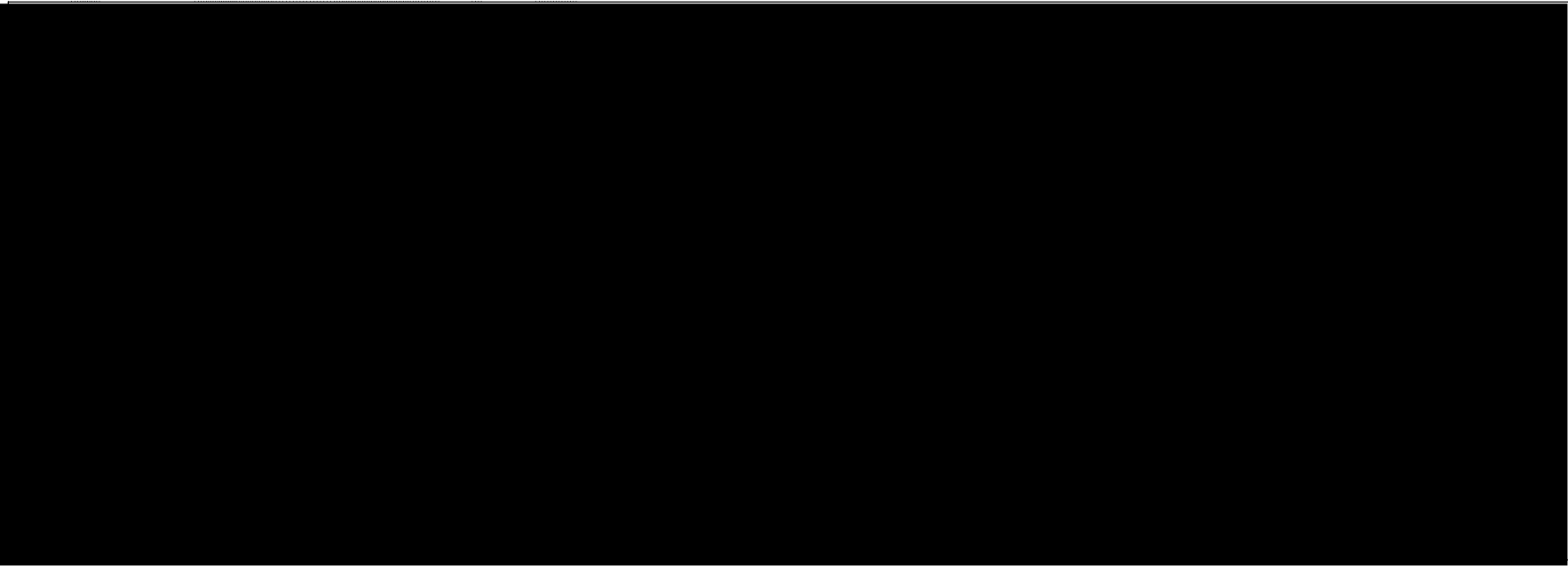
The Canadian Adverse Events Following Immunization Surveillance System (CAEFISS) is a federal, provincial and territorial public health post-market vaccine safety surveillance system. CAEFISS is managed by the Public Health Agency of Canada (PHAC).

Up to and including 25 June 2021, 8570 adverse events following immunization (AEFIs) were reported to the Canada Vigilance Program and CAEFISS in Canada.⁴ Of these 1884 were serious.

⁴ <https://health-infobase.canada.ca/covid-19/vaccine-safety/>

Start of Confidential Information

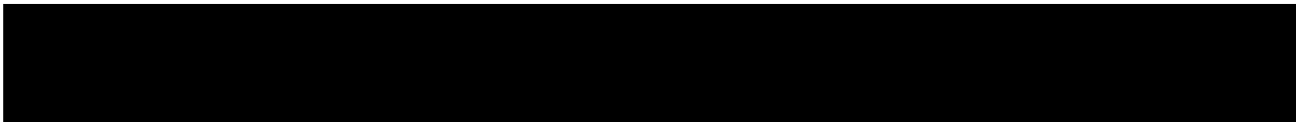
Reports from the CAEFISS database up to July 05, 2021, as analyzed by the PHAC showed a statistical disproportional signal in all 5 statistical signal detection methods for a number of events.



End of Confidential Information

7 SIGNIFICANT FINDINGS FROM STUDIES OR OTHER SOURCES DURING THE REPORTING PERIOD

The SMSR did not include significant findings from completed and ongoing clinical trials, non-interventional studies, non-clinical data, and other periodic reports.



8 LATE-BREAKING INFORMATION

The section was not provided in this SMSR.

Actions taken for safety reasons by regulatory agencies

Based on data collected following mass immunization, the FDA, the MHRA and Health Canada requested a labelling update on June 25, 2021, to include a warning statement regarding the risk of myocarditis and/or pericarditis following immunization with mRNA COVID vaccines. The Pfizer BioNtech CPM was updated on 30 June 2021.

Following the review of the EU-RMP V2.0 and Canadian Addendum (DSTS# 253040) on June 07, 2021, the MAH was also requested to include myocarditis and pericarditis in the Canadian risk management plan and update the pharmacovigilance plan accordingly.

Start of Confidential Information

The EMA will be requesting a similar update as was done in other jurisdictions as well as an update in the RMP following the July 05-08, 2021 PRAC meeting.

End of Confidential Information

9 OVERVIEW OF SIGNALS DISCUSSED BY THE MAH: NEW, ONGOING, OR CLOSED

During the reporting period, 10 signals were evaluated by the MAH and closed during the reporting period:

Safety topic	Safety Trigger/ MAH's Assessment	MHPD comments
Appendicitis	Health Canada request/ Evidence does not support a causal association- Signal closed	

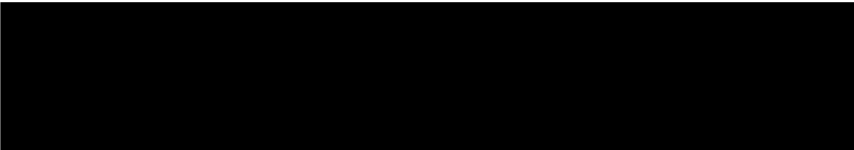
Dizziness	MHRA request/ The available information supports dizziness associated with the vaccination process (i.e. stress related response) but not a causal association with the vaccine itself at this time- Signal Closed	<p>From safety evaluation data reported under Appendix 3.7:</p> <p>Clinical trials</p> <p>The MAH notes that “Dizziness” was reported in 78 participants (0.4%) in the BNT162b2 group compared with 60 participants in the placebo group (AEs reported from Dose 1 to 1 month post dose 2 during the blinded controlled follow up period). Postural dizziness was reported by 2 (0.0%) BNT162b2 recipients and 1 (0.0%) placebo recipient.</p> <p>Post market cases (up to 30 April 2021) using MedDRA PT Dizziness</p> <ul style="list-style-type: none">e. A total of 15,260 cases were reported for BNT162b2.f. Median Age was 46. Most frequent reported age was between 31-50 years oldg. Approximately 40% of the cases occurred within the first 24 hours. Co-reported events were most commonly reactogenicity events. The most common were headache (2718), nausea (2097), asthenia (1216), and chills (1130)h. There were 8 events of dizziness with a fatal outcome. 4 cases with a latency of Day 0. Of these, 3 cases were in patients between 80-94 years of age with a medical history of neurological and cardiac manifestations), 1 case with a fatal outcome with latency of Day 2, a 27 year-old male experienced dizziness and vomiting blood 2 days after vaccination. <p>As per the Summary of the MAH’s assessment/conclusion: because dizziness is a term commonly used by patients to describe symptoms that are inconsistently defined, and based on the postauthorization reports, it is plausible that the dizziness experienced soon after vaccination is a potential manifestation of vaccination-related situational stress, anxiety and/or is confounded by the systemic reactogenicity experienced in the same time period. Cases of dizziness that described an inability to drive were relatively rare (11). Additionally, in the course of the Phase 2/3 clinical trials, events of dizziness were not meaningfully different in the active cohort (0.4%) compared to placebo cohort (0.3%).</p> <div></div>
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<p>Myocarditis/ pericarditis</p>	<p>Signal ongoing</p>	<p>The MAH retrieved 495 reports of myocarditis and pericarditis (up to May 25, 2021). Of the 495, there were 260 cases of myocarditis (all assessed as serious), 73 met a certainty in diagnosis of myocarditis when assessed based on the Brighton’s Collaboration (BC) diagnostic certainty criteria. 18 cases Eighteen (18) cases were classified as BC Level 1 (confirmed), 24 cases as BC level 2 (probable), 31 cases as BC level 3 (possible).</p> <p>The majority of the confirmed, probable and possible myocarditis case reports were in younger age groups below 39 years of age (48/73; 66%). None had a fatal outcome. There were more males than females. 2 cases assessed as possible myocarditis were from Canada.</p> <p>MAH’s assessment/conclusion: The rate at which these events are reported (even without applying the diagnostic certainty criteria) do not exceed the expected background rate. It should be noted that with the case information currently available, only 18 (6.9%) of the cases could be assessed as “confirmed cases” of myocarditis as per Brighton Collaboration criteria. It is worth noting that the incidence rate of myocarditis in COVID-19 infected patients is 2.3 out of 100 in a recovering population. Given the totality of the data, a causal association between the vaccine and myocarditis or pericarditis cannot be established. The MAH will continue to perform robust pharmacovigilance, follow up, and monitoring of this topic.</p> <div></div>
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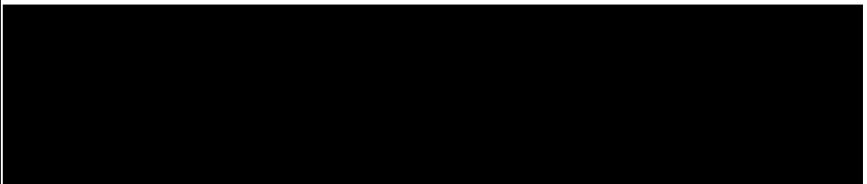
Safety topic	Safety Trigger/ MAH's Assessment	MHPD comments
Abnormal behaviour/mental disorder	Japan PMDA/No validated signal	<p>The MAH did not provide the assessment regarding abnormal behaviour in the monthly safety report #6; however, the MAH concluded that the available data do not support this topic as a validated signal.</p>
Acquired Hemophilia	Request from France ANSM/No Validated Signal	<p>The MAH did not provide the assessment regarding acquired hemophilia in the monthly safety report #6; however, the MAH concluded that the available data do not support this topic as a validated signal. The MAH noted that the ANSM 15th PV report of AEs found 3 cases of acquired hemophilia since the start of vaccination and considered it as a potential signal. A review of the small number of post-authorization AE reports of acquired hemophilia was undertaken and this topic was determined not to be a validated signal.</p>
Acute disseminated Encephalomyelitis (ADEM)	PRAC request/No Validated Signal	<p>The MAH notes that ADEM has been described most frequently following measles mumps and rubella vaccinations, but at a lower incidence of ADEM after a wild-type measles encephalitis. Other reports of ADEM have been described both after H1N1 infection and H1N1 vaccination.</p> <p>Post-marketing cases</p>

		<p>-78 cases were reported including one case from a Pfizer-sponsored interventional study.</p> <p>-majority of cases (64/78) were medically confirmed.</p> <p>-Median reported age 51.5, mean 54.2 years</p> <p>- Of the 78 reports, 48 (61.5%) were reported as females, 29 (37.2%) as males, and in 1 (1.3%) case sex was not reported</p> <p>-Most cases were from the US (18) and UK (14), France and Spain (6 each)</p> <p>-Time to onset (reported in 58 cases) ranged between 2 to 21 days in 43 cases. 12 cases reported time to onset as the same vaccination day or day after. In 3 cases time to onset was reported as 22, 28 and 38 days post-vaccination.</p> <p>- Case outcome was reported as recovered/recovering/recovered with sequelae in 33 cases (42.3%), not recovered at time of reporting in 28 cases (35.9 %), and outcome was unknown in 11 cases (14.1%) .There were also 6 fatal cases (7.7%).</p> <p>-All cases were assessed according to BC criteria. None of the cases met BC level 1. 75 cases were assessed as follows:</p> <ul style="list-style-type: none">• 7 cases (9.2%) met level 2;• 11 cases (14.5%) met level 3;• 41 cases (55.3%) met level 4 (reported encephalitis/ADEM with insufficient evidence to meet the case definition);• 16 cases (21%) met level 5 (not a case of encephalitis/ADEM) <p>Among the 59 cases that met BC level 2,3 4, alternative explanations including previous disease/neurologic co-morbidities were reported.</p> <p>Of note, the MAH revised the observed to expected ratio based on a background rate of 5.3 per 100,000 person years to better align with the spontaneously reported case definition. In the previous SMR the MAH used a background rate of 0.1 from the ACCESS initiative.</p> <p>According to the MAH, given the totality of the available information, this review of the data did not support validation of a signal. Changes in the risk minimization measures or updates to the product information label are not warranted at this time. The benefit risk profile of the vaccine remains favorable. The topic will continue to be closely monitored.</p> <div></div>
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Safety topic	Safety Trigger/ MAH's Assessment	MHPD comments
Acute pancreatitis	Request from France ANSM/ No Validated Signal	<p>The MAH did not provide the assessment regarding acute pancreatitis in the monthly safety report #6; however, the MAH concluded that the available data do not support this topic as a validated signal. The MAH noted that the ANSM 14th PV report of AEs found 19 cases of acute pancreatitis since the start of vaccination and considered it as a potential signal. A review of the AE reports of acute pancreatitis was undertaken and this topic was determined not to be a validated signal.</p> <div></div>

Safety topic	Safety Trigger/ MAH's Assessment	MHPD comments
Guillain-Barre Syndrome	Request from France ANSM/No Validated Signal	<p>Post market cases</p> <p>The MAH retrieved 147 cases from their database (up to May 10, 2021):</p> <ul style="list-style-type: none"> -76 females and 67 males -Age range between 18 to 97 years, mean 59.3 years - Most of the cases were reported from US (36, 24.5%), United Kingdom (30, 20.4%) followed by Japan (12, 8.2%). -The outcome of the event was reported as not recovered at time of reporting in 53 cases (36.1%), as recovering/resolving in 53 cases (36.0 %), and as unknown in 36 cases (24.5%) and fatal in 5 cases (3.4%) - Time to onset ranged from same vaccination day to 63 days following vaccination, with the majority of cases reported within 7 days of vaccination. <p>All cases have been assessed according to BC criteria as follows:</p> <ul style="list-style-type: none"> • 4 case (2.7 %) met level 1 • 16 cases (10.8 %) met level 2 • 1 case (0.7 %) met level 3 • 116 cases (79 %) met level 4 • 9 cases (6.1 %) met level 5 • 1 case (0.7%) was referring to another vaccine <p>Medical history found confounding factors in 33 cases (cerebrovascular accident (2), Chronic inflammatory demyelinating polyradiculoneuropathy (4), autoimmune disease, HIV and Cancer (14), Covid-19 infection (3 cases), symptoms in 1 case were pre-existing vaccination.</p> <p>MAH's assessment/ conclusion: Most reported cases (79%) met level 4 of BC. Most cases meeting BC level 1 or 2 were confounded by preceding infection, implausible time to onset, symptoms pre-existing vaccination or GBS in the context of cerebral infarct. The upper limit of the 95% confidence interval for the observed to expected ratio did not exceed 1; therefore, a signal was not identified. Overall, given the totality of the available information, GBS is not considered to be a validated signal, changes in the risk minimization measures or updates to the product information label are not warranted at this time. The benefit risk profile of the vaccine remains favorable.</p> 

Safety topic	Safety Trigger/ MAH's Assessment	MHPD comments
Menstrual cycle abnormalities	Request from Israel Ministry of Health/ No Validated Signal	<p>The MAH noted a review of menstrual terms from the clinical study data and from the postauthorization AE reports was undertaken. The available data did not support a validated signal.</p> <div></div>

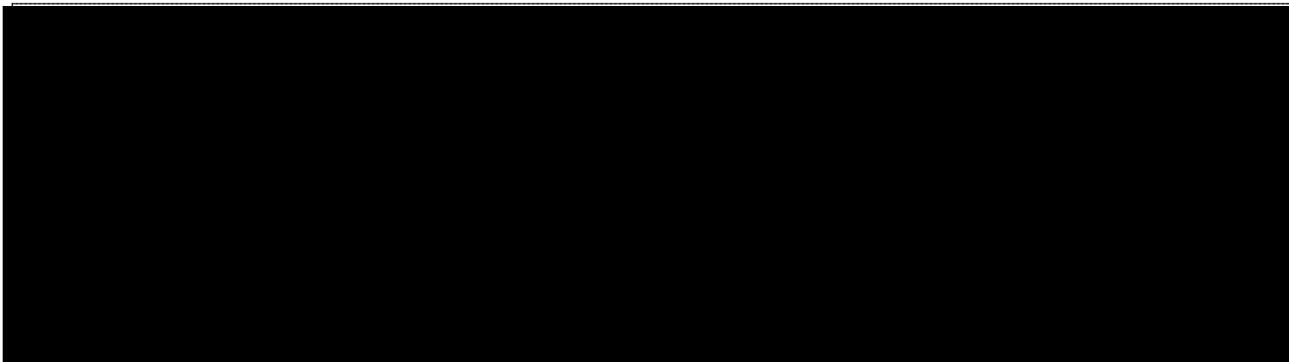
Safety topic	Safety Trigger/ MAH's Assessment	MHPD comments
Transverse myelitis	Request from Australia TGA/ No validated signal	<p>The MAH noted several case reports describing transverse myelitis in temporal relationship with Coronavirus infection have been published. The reported time to onset was between 8 days to 3 weeks upon infection symptoms.</p> <p><u>Post-market (data as of 17 May, 2021)</u></p> <ul style="list-style-type: none"> -67 cases identified. All cases were assessed as serious. -51 females, 15 males, and in one case gender was not reported. -Age range between 21 to 84 years (mean 48, median 43) -Most of the cases were reported from UK (23, 34.3%), followed by United States (20, 29.9%). -The outcome of the event was reported as not recovered at time of reporting in 30 cases (44.8%) resolving/recovering in 25 (37.3%) and unknown in 15 cases (17.9%).. All cases have been assessed according to BC criteria as follows: <ul style="list-style-type: none"> • 0 cases (0%) met level 1 • 2 cases (3%) met level 2 • 5 cases (7.5%) met level 3 • 53 cases (79.1%) met level 4 • 7 cases (10.4%) met level 5 - Time to onset was reported for 34 cases and ranged from the same vaccination day to 21 days after vaccination. - Unadjusted observed to expected ratio (O/E) analyses were conducted for the 67 reported TM cases. The O/E ratio was above 1 for the 21-day risk window and below 1 for the no risk window, indicating there may be an increased risk of TM among recipients of the BNT162b2 vaccine. <p>MAH's conclusion/assessment: The E/O analysis showed a small increase over the 21 days risk window nevertheless, as described in the O/E analysis the 21-day risk window is particularly conservative as all observed cases are included in the numerator of the O/E ratio regardless of the days since vaccination dose, which will lead to an overestimation of the ratio if observed cases occurred outside of the risk window. In addition, the ACCESS background rate used to calculate the expected number of cases is derived from medical records coded as transverse myelitis or acute transverse myelitis while the observed cases were identified in the spontaneous reporting system using a broader search criteria (as specified in the method). Updates to the product information label is not warranted at this time.</p> 

10 REVIEW OF NEW SAFETY INFORMATION

10.1 SUMMARY OF SAFETY CONCERNS

The summary of safety concerns for the Pfizer-BioNTech COVID-19 Vaccine can be found below. This summary includes ongoing safety concerns from both the European RMP (EU RMP) version 1.1 dated 15 April 2021, the US Pharmacovigilance Plan (PVP) version 0.4 dated 08 April 2021 and the South Africa RMP version 1.0 dated 24 March 2021.

Important identified risk	Anaphylaxis
Important potential risk	Vaccine-Associated Enhanced Disease (VAED), including Vaccine-Associated Enhanced Respiratory Disease (VAERD)
Missing information	Use in pregnancy and while breast feeding
	Use in immunocompromised patients
	Use in frail patients with co-morbidities (e.g., COPD, diabetes, chronic neurological disease, cardiovascular disorders, active tuberculosis)
	Use in patients with autoimmune or inflammatory disorders
	Interaction with other vaccines
	Long-term safety data
	Use in paediatric individuals <12 years of age
	Vaccine effectiveness



10.2 SUMMARY OF ADVERSE EVENTS OF SPECIAL INTEREST

The search criteria for the adverse events of special interest (AESIs) for the Pfizer-BioNTech COVID-19 Vaccine can be found in Appendix **Error! Reference source not found.** The list of AESIs takes into consideration AESIs from expert groups and regulatory authorities, including the Brighton Collaboration.

10.2.1 Adverse events of special interest (AESI)

Pfizer provided cumulative assessment for AESI(s) noted in the table below, and did not validate any signals or identify new risks emerging from their analysis. No further action was proposed, standard surveillance is applied.

AESI Category	MAH's assessment	MHPD comments
Anaphylactic Reactions <i>Search criteria:</i> <i>Anaphylactic reaction SMQ (Narrow and Broad, with the algorithm applied), selecting relevant cases according to BC criteria</i>	No signal	Anaphylaxis is labelled in the CPM under Warnings and Precautions. No new safety concerns based on the information provided, no further regulatory action is recommended at this time.

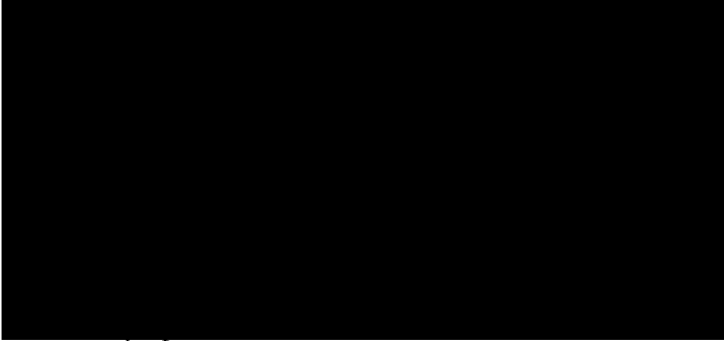
<p>Cardiovascular AESIs <i>Search criteria: PTs</i> <i>Acute myocardial infarction;</i> <i>Arrhythmia; Cardiac failure; Cardiac failure acute; Cardiogenic shock; Coronary artery disease; Myocardial infarction; Postural orthostatic tachycardia syndrome; Stress cardiomyopathy; Tachycardia</i></p>	<p>No signal</p>	<p>Number of cases: 1585 (3.4 % of the total PM dataset, compared to 2.8% in the previous reporting period) 1217 medically confirmed and 368 are non-medically confirmed; - age (n = 1502): ranged from 16 to 101 years (mean = 50.8 years, median = 46 years); -Subjects' age group (n = 1514): Adult36 (1088), Elderly (422) and Adolescent (4); -Reported relevant PTs: Tachycardia (1093), Arrhythmia* (177), Myocardial infarction* (170), Cardiac failure* (87), Acute myocardial infarction* (66), Cardiac failure acute* and Cardiogenic shock* (13 each), Coronary artery disease* and Postural orthostatic tachycardia syndrome* (10 each), Stress cardiomyopathy* (6). - Outcome:39 resolved/resolving (727), not resolved (182), fatal (119), resolved with sequelae (22) and unknown (596); -Median time to onset is 24 hours following vaccination.</p> <p>MAH's conclusion/assessment: No cardiovascular signals have emerged from the review of post-authorisation data. The review of cases and O/E analysis do not raise new concerns. Safety surveillance will continue.</p> <div></div>
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AESI Category	MAH's assessment	MHPD comments
COVID-19 AESIs <i>Search criteria: Covid-19 SMQ (Narrow and Broad) OR PTs Ageusia; Anosmia</i>	No signal	No new safety concerns based on the information provided, no further regulatory action is recommended at this time
Dermatological AESIs <i>Search criteria: PT Chillblains; Erythema multiforme</i>	No signal	No new safety concerns based on the information provided, no further regulatory action is recommended at this time. There are currently a total of <u>11 cases</u> reported following the Pfizer BioNtech vaccine in the Canadian databases (report published July 5, 2021). Chillbains and Erythema multiform are closely monitored by the MHPD and PHAC and are included in the AESIs for COVID vaccines.

AESI Category	MAH's assessment	MHPD comments
Facial Paralysis <i>Search criteria: PTs</i> <i>Facial paralysis, Facial paresis, Oculofacial paralysis</i>	No signal	

⁵ https://www.ema.europa.eu/en/documents/product-information/comirnaty-epar-product-information_en.pdf

⁶ <https://www.fda.gov/media/144413/download>

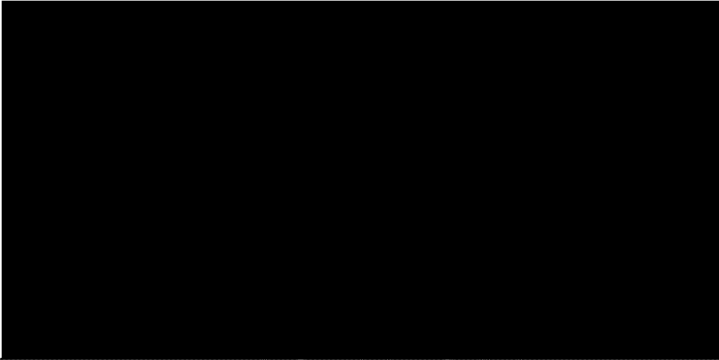
AESI Category	MAH's assessment	MHPD comments
<p>Haematological AESIs <i>Search criteria:</i> <i>Leukopenias NEC (HLT)</i> <i>OR Neutropenias (HLT)</i> <i>OR PTs Immune thrombocytopenia, Thrombocytopenia OR SMQ Haemorrhage terms (excl laboratory terms)</i></p>	No signal	<p>Most frequently reported relevant PTs (10 occurrences) include: Heavy menstrual bleeding (323), Contusion (227), Epistaxis (196), Thrombocytopenia* (186), Haemorrhage* (121), Vaginal haemorrhage (104), Vaccination site bruising (73), Petechiae (70), Intermenstrual bleeding (68), Immune thrombocytopenia* (57), Vaccination site haematoma (52), Haematoma (51), Purpura (46), Haematochezia (42), Vaccination site haemorrhage (41), Eye haemorrhage, Postmenopausal haemorrhage and Rectal haemorrhage (34 each), Conjunctival haemorrhage and Haematuria (27 each), Blood urine present (24), Ecchymosis, Haemoptysis and Internal haemorrhage (22 each), Gingival bleeding (21), Neutropenia (18), Gastrointestinal haemorrhage (15), Lymphopenia (14), Diarrhoea haemorrhagic, Haematemesis and Haemorrhage subcutaneous (13 each) and Blood blister, Leukopenia and Subdural haematoma (12 each)</p> 
<p>Musculoskeletal AESIs <i>Search criteria: PTs Arthralgia; Arthritis; Arthritis bacterial; Chronic fatigue syndrome; Polyarthritis; Post viral fatigue syndrome; Rheumatoid arthritis</i></p>	No signal	<p>No new safety concerns based on the information provided, no further regulatory action is recommended at this time.</p>

AESI Category	MAH's assessment	MHPD comments
Neurological AESIs (including demyelination) <i>Search criteria:</i> <i>Convulsions (SMQ) (Broad and Narrow) OR Demyelination (SMQ) (Broad and Narrow) OR PTs Ataxia; Cataplexy; Encephalopathy; Fibromyalgia; Intracranial</i>	No signal	<p>Most frequently reported relevant PTs (≥ 5 occurrences) included: Seizure* (236), Neuropathy peripheral* (101), Epilepsy (84), Guillain-Barre syndrome* (60), Generalised tonic-clonic seizure* (38), Fibromyalgia* (30), Febrile convulsion* and Multiple sclerosis* (23 each), Trigeminal neuralgia (22), Status epilepticus (16), Optic neuritis* (15), Multiple sclerosis relapse* (13), Ataxia (12), Myelitis transverse* (11), Tongue biting (8), Polyneuropathy (7), Acute disseminated encephalomyelitis*, Aura, Meningitis*, Meningitis aseptic*, Partial seizures*, Seizure like phenomena (6 each), Clonic convulsion, Intracranial pressure increased and Petit mal epilepsy (5 each);</p> <p>6 serious cases were reported in Canada in the current interval.</p>
Hepatic AESIs <i>Search criteria: Liver related investigations, signs and symptoms (SMQ) (Narrow and Broad) OR PT Liver injury</i>	No signal	No new safety concerns based on the information provided, no further regulatory action is recommended at this time
Immune-Mediated/Autoimmune AESIs <i>Search criteria: Immune mediated/autoimmune disorders (SMQ) (Broad and Narrow) OR Autoimmune disorders HLGT OR PTs Cytokine release syndrome; Cytokine storm; Hypersensitivity</i>	No signal	No new safety concerns based on the information provided, no further regulatory action is recommended at this time

<p>Pregnancy Related AESIs <i>Search criteria: PTs Amniotic cavity infection; Caesarean section; Congenital anomaly; Death neonatal; Eclampsia; Foetal distress syndrome; Low birth weight baby; Maternal exposure during pregnancy; Placenta praevia; Pre-eclampsia; Premature labour; Stillbirth; Uterine rupture; Vasa praevia</i></p>	<p>No signal</p>	<p>The MAH provided a cumulative analysis regarding the outcome of reported pregnancies.</p> <p>Cumulatively a total of 995 unique pregnancies were reported, 317 of which were received during the reporting interval.</p> <p>Overall, the majority (763) of these cases had insufficient information to conduct a meaningful medical assessment of causality (e.g., concomitant medications, trimester of exposure, pregnancy outcome, medical history). Of the 1036 cases reported cumulatively, 478 were assessed as serious. The most frequently reported pregnancy related events in these cases coded to the PTs Abortion spontaneous (187), Abortion missed (19), Foetal death (16), Premature baby (13), Foetal growth restriction (10), and Abortion (6).</p> <p>MAH’s conclusion: The review of the cases indicative of drug exposure during pregnancy did not reveal any new safety information.</p> <p>The MAH is conducting a post-authorization study (C4591015) to study the safety of the vaccine in pregnancy.</p> <div></div>
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AESI Category	MAH's assessment	MHPD comments
Renal AESIs <i>Search criteria: PTs Acute kidney injury; Renal failure.</i>	No signal	No new safety concerns based on the information provided, no further regulatory action is recommended at this time
Respiratory AESIs <i>Search criteria: Lower respiratory tract infections NEC (HLT) OR Respiratory failures (excl neonatal) (HLT) OR Viral lower respiratory tract infections (HLT) OR PTs: Acute respiratory distress syndrome; Endotracheal intubation; Hypoxia; Pulmonary haemorrhage; Respiratory disorder; Severe acute respiratory syndrome</i>	No signal	No new safety concerns based on the information provided, no further regulatory action is recommended at this time

AESI Category	MAH's assessment	MHPD comments
<p>Thromboembolic Events <i>Search criteria: Embolism and thrombosis (HLGT), excluding PTs reviewed as Stroke AESIs, OR PTs Deep vein thrombosis; Disseminated intravascular coagulation; Embolism; Embolism venous; Pulmonary embolism</i></p>	<p>No signal</p>	<p>Most frequently reported relevant PTs (≥5 occurrences) included: Pulmonary embolism* (588), Deep vein thrombosis* (442), Thrombosis (339), Thrombophlebitis superficial (65), Thrombophlebitis (53), Venous thrombosis limb (37), Embolism(36), Pulmonary thrombosis (35), Venous thrombosis (24), Retinal vein occlusion (21), Retinal artery occlusion and Portal vein thrombosis (17 each), Mesenteric vein thrombosis (14), Retinal vein thrombosis (13), Jugular vein thrombosis and Peripheral artery thrombosis (11 each), Pelvic venous thrombosis (10), Arterial thrombosis, Intracardiac thrombus, Ophthalmic vein thrombosis and Subclavian vein thrombosis (8 each), Coronary artery thrombosis (7), Embolism venous and Pulmonary artery thrombosis (6), Retinal artery thrombosis (5);</p> <p>There were 23 cases of thromboembolic events reported in the current interval in Canada</p> <div></div>

AESI Category	MAH's assessment	MHPD comments
Stroke <i>Search criteria: HLT Central nervous system haemorrhages and cerebrovascular accidents (Primary Path) OR HLT Cerebrovascular venous and sinus thrombosis (Primary Path)</i>	No signal	<p>Most frequently reported relevant PTs (≥ 5 occurrences) included:</p> <ul style="list-style-type: none"> o PTs indicative of Ischaemic stroke: Cerebrovascular accident* (308), Ischaemic stroke* (144), Cerebral infarction* (106), Cerebral venous sinus thrombosis* (35), Cerebral thrombosis* (22), Cerebral ischaemia (18), Embolic stroke (14), Thrombotic stroke* (9), Cerebral artery embolism, Cerebral venous thrombosis and Ischaemic cerebral infarction (8 each), Brain stem infarction and Cerebral artery occlusion (6 each) and Carotid artery occlusion, Carotid artery thrombosis, Cerebellar stroke, Cerebral artery thrombosis and Lacunar infarction (5 each); o PTs indicative of Haemorrhagic stroke: Cerebral haemorrhage* (93), Subarachnoid haemorrhage* (32), Haemorrhagic stroke* (18), Cerebral haematoma*, Haemorrhage intracranial* and Haemorrhagic transformation stroke (6 each); <p>8 cases were reported in Canada in the current interval.</p> 
Vasculitic Events <i>Search criteria: Vasculitides HLT</i>	No signal	<p>No new safety concerns based on the information provided, no further regulatory action is recommended at this time.</p>

10.3 SUMMARY OF SPECIAL SITUATIONS

10.3.1 Special situations

Overall, the MAH did not identify new safety signal from the evaluation of special situations (Death, Lack of Efficacy and Vaccine Interactions). : Causes of death most frequently reported (>2% of total fatal cases): Death (198), COVID-19 (76), Cardiac arrest (72), Sudden death (63), Dyspnoea (58), Pulmonary embolism (56), Cardio-respiratory arrest (49), Myocardial infarction (45), Vaccination failure (41), Pyrexia (39), COVID-19 pneumonia (35), Respiratory failure (34), Cerebrovascular accident, Drug ineffective (31 each), Cerebral haemorrhage, Pneumonia (29 each), Cardiac failure (23), and Vomiting (20).

11 EFFECTIVENESS STUDIES

As noted by the MAH, a statistically greater response was achieved in Study 2 in the adolescents 12 to 15 years of age compared to participants 16 to 25 years of age to demonstrate a non-inferior immune responses:

The geometric mean titers (GMT) ratio of the adolescents 12 to 15 years of age group to the participants 16 to 25 years of age group was 1.76, with a 2-sided 95% CI of 1.47 to 2.10, meeting the 1.5-fold non-inferiority criterion (the lower bound of the 2-sided 95% CI for the geometric mean ratio [GMR] > 0.67) which indicates a statistically greater response in the adolescents 12 to 15 years of age than that of participants 16 to 25 years of age.

12 OTHER SAFETY CONCERNS AND FOLLOW-UPS

11.1. Responses to MHPD following the assessment of the April monthly safety report

In accordance with the Risk Management Plan Terms and Conditions, imposed under the Interim Order Respecting the Importation, Sale and Advertising of Drugs for Use in Relation to Covid-19, Pfizer Canada ULC is required to submit monthly safety reports for the period of the Interim Order authorization. As such, you are requested to submit the monthly safety report for the period of April 30, 2021 to May 31, 2021 including cumulative number of reports (serious and non-serious) and adverse events that occurred in Canada and globally for the Pfizer-BioNTech COVID-19 Vaccine (tozinameran) known to Pfizer Canada ULC and BioNTech Manufacturing GmbH. Actions for Pfizer Canada ULC and BioNTech Manufacturing GmbH stemming from the SMSR #5 review are to:

Comment 1

Discuss the need to submit a new Post-Authorization change – PM safety update and/or update the risk management plan regarding the following risks:

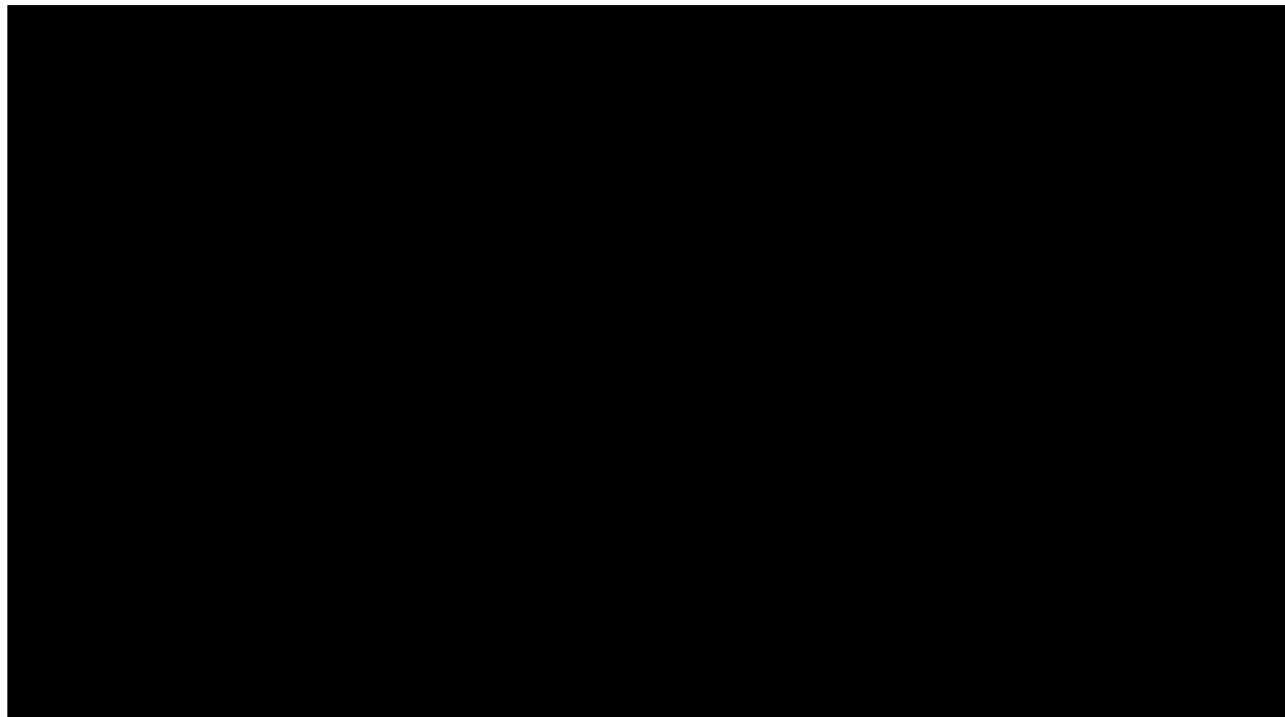
Facial paralysis /Bell's Palsy in association with the Pfizer-BioNTech COVID-19 Vaccine, based on the imbalance observed in the clinical trials, increase in frequency of reporting from the post-market data, and safety information captured in the EMASmPC and EUA USPI (including Bell's Palsy).

Myocarditis/Pericarditis in association with the Pfizer-BioNTech COVID-19 Vaccine- based on the following:

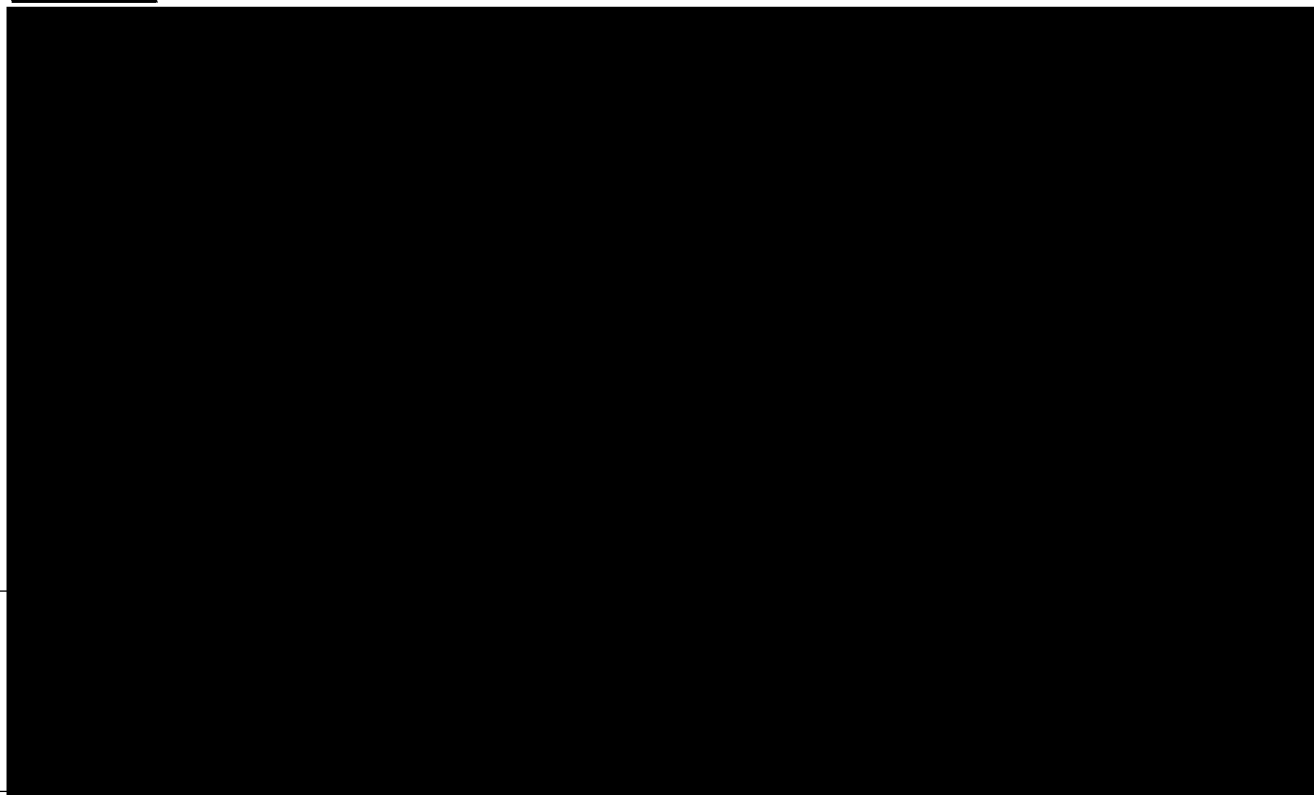
substantive number of cases that met the Bonaca criteria for definite, probable and possible myocarditis in the SMSR #5 most events are temporally related to the vaccination

Israel Ministry of Health¹ concluded a possible link between the second dose and the onset of myocarditis among young men (16-30), and that this link was highlighted to be stronger among the 16-19 younger age group.

that adolescents and the young adult population will soon be vaccinated in much larger numbers.

Response 1:**Comment 2**

Discuss the timeline for alignment of the Reference Safety Information and the Canadian Product Monograph for the following events: Asthenia, Lethargy, Decreased appetite, Hyperhidrosis, Night sweats and Paresthesia. In addition, address any plans to include labelling updates from other jurisdictions, such as facial swelling in people with a history of injections with dermal fillers recommended by the European Medicines Agency.

Response 2:**Comment 3**

In addition, please include the following in the next SMSR:

Provide an updated cumulative review of the following safety topics. Data should be stratified by sex, age, gender, dose 1 or dose 2 and assessed for causality using Brighton Collaboration Definition Criteria (or validated Definition Criteria). The observed and expected analyses should be included. An analysis of Canadian cases should be included. In addition, discuss the need for any potential amendment to the product monograph and/or the risk management plan and make, accordingly, a proposal for the changes to the relevant sections within this discussion.

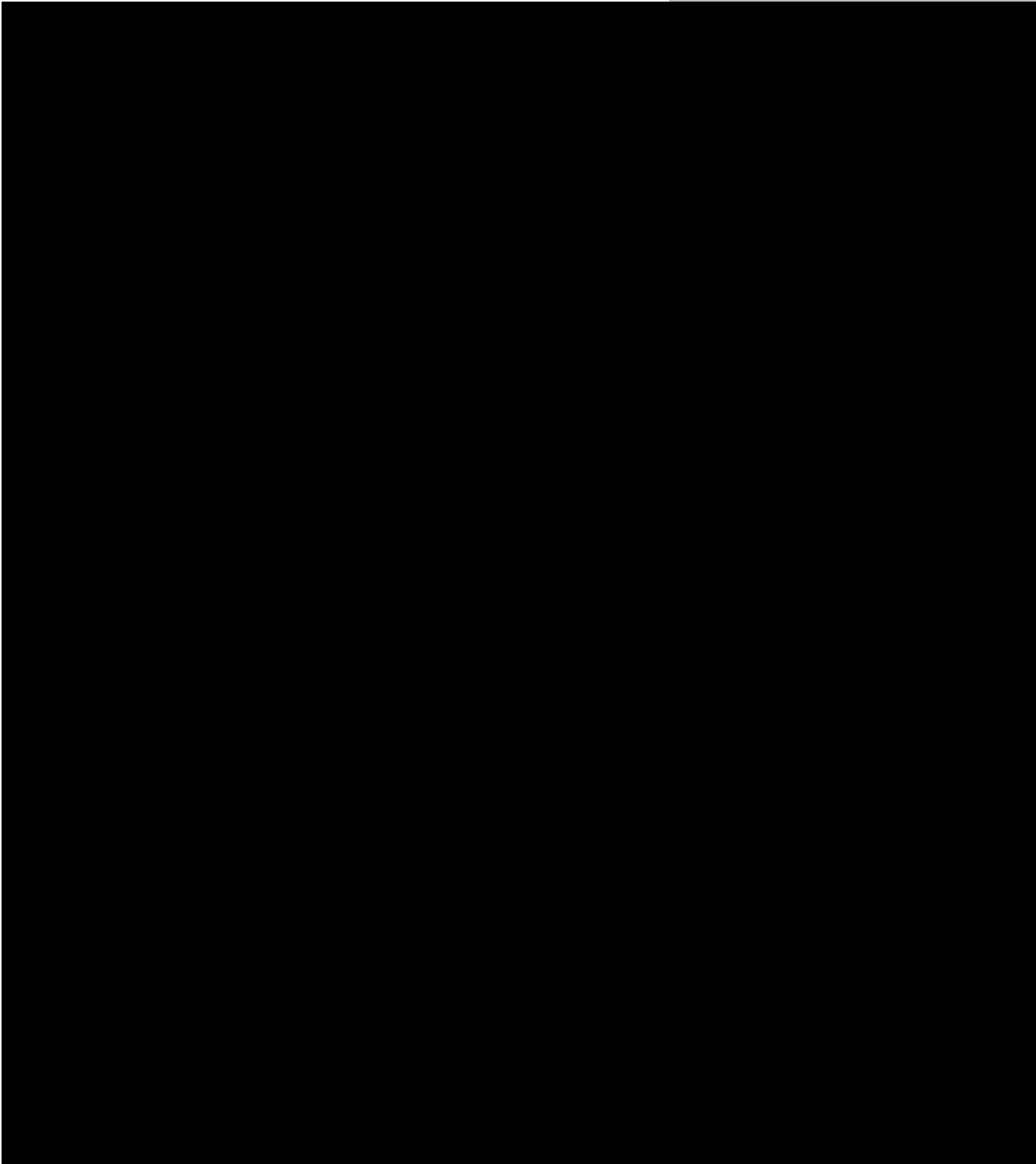
Cases of thrombosis with thrombocytopenia following vaccination with Pfizer BioNtech using appropriate SMQs to extract the cases including: thrombotic events with/without thrombocytopenia and thrombocytopenia without applying time limit specifications.

Cases of seizure following vaccination of Pfizer BioNtech vaccine. Search criteria should be included and encompass all generalized convulsive seizures following immunization.

Cases of hypertensive crisis with intracranial haemorrhage and provide a discussion regarding cases recently described in the literature.

Cases of hearing loss and trigeminal neuralgia, and provide a discussion regarding cases recently analyzed.

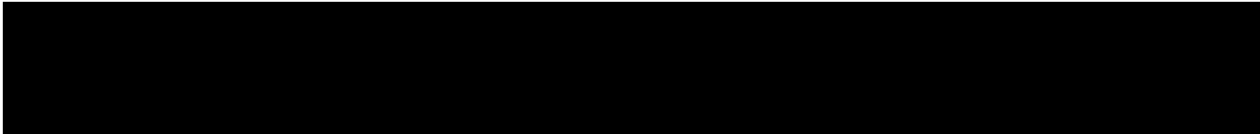
Response 3:



13 TERMS AND CONDITIONS

As stated in section 2, the Pfizer-BioNTech COVID-19 Vaccine is subject to terms and conditions that need to be met by the MAH. The compliance of the MAH to the terms and conditions relevant to adverse events reporting will be assessed below.

Terms and conditions	Met or not met
The monthly safety reports should be submitted within 15 days after the last day of a month, beginning after the first full calendar month after authorization.	
Interval and cumulative number of reports (serious and non-serious), overall and by age groups and in special populations (e.g. pregnant women)	
Interval and cumulative number of reports per HLT and SOC	
Number of reports in Canada and Global	
Exposure data, stratified by country, age groups, race and ethnicity	
Changes to reference safety information in the interval	
Ongoing and closed signals in the interval	
List of adverse events of special interest including the Safety Platform for Emergency Vaccines list and RMP safety concerns (including the additional missing information): reports – numbers and relevant cases, including time-to-onset and O/E analyses	
Fatal reports – numbers and relevant cases, including observed/expected analyses	
Vaccination failure / lack of efficacy (including confirmed and suspected cases) and errors – number relevant cases	
Potential interaction with other vaccines/concomitant treatments-number and relevant cases	
Summary outcomes of some of the routine pharmacovigilance activities (as presented in the EU RMP Part III and applied in the Canadian context) should be included for the purpose of rapid signal detection and communication activities. Summary of all ongoing studies can be included in the first six-month scheduled PBRER, unless a safety signal is identified that requires immediate regulatory action.	
Risk/benefit considerations	

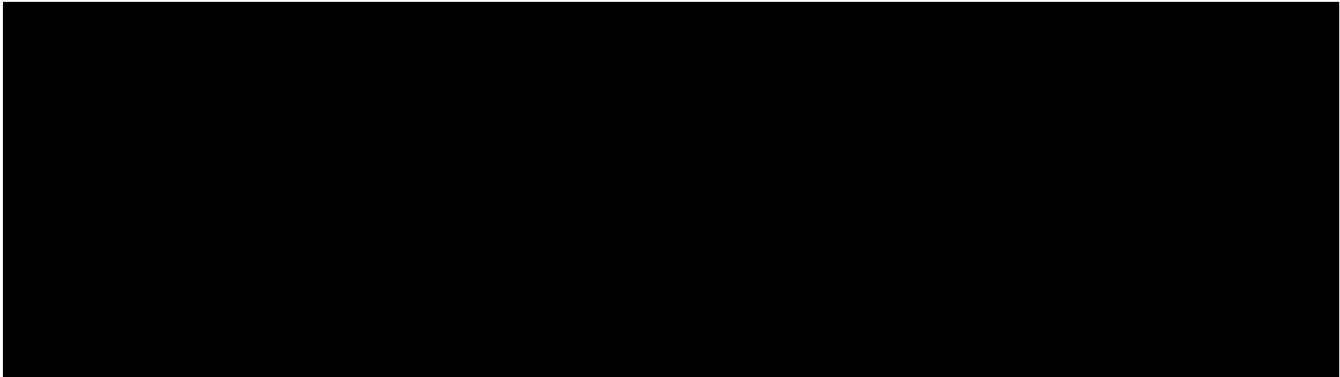


14 COMPLIANCE ISSUES (GVP/GMP)

The section was not provided in this SMSR.

15 RECOMMENDATIONS

Please refer to Executive Summary for recommendations to the MAH, BRDD and MHPD.



16 REFERENCES

The references are provided as footnotes and hyperlinks throughout the document.

17 APPENDICES



Health Santé
Canada Canada

**Health Products and Food Branch
Direction générale des produits de santé et des aliments**

Marketed Health Products Directorate	The Marketed Health Products Directorate (MHPD) is responsible for coordination of consistency of post-market surveillance and assessment of signals and safety trends concerning all marketed health products.
Direction des produits de santé commercialisés	La Direction des produits de santé commercialisés (DPSC) est chargée de la coordination et la cohérence des activités de surveillance post-approbation et d'évaluer les signaux et les tendances concernant l'innocuité de tous les produits de santé commercialisés.

MEMORANDUM

NOTE DE SERVICE

TO : Leo Bouthillier, PhD
À Director
Centre for Evaluation of
Radiopharmaceuticals and
Biotherapeutics (CERB)
Biologic and Radiopharmaceutical
Drugs Directorate (BRDD)

FROM : Melissa Hunt
DE Director
Marketed Health Products
Directorate (MHPD)

SECURITY - CLASSIFICATION - DE SÉCURITÉ
Protected B
OUR FILE - NOTRE RÉFÉRENCE
Control number: 251813 and 253419
YOUR FILE - VOTRE RÉFÉRENCE
DATE
July 12, 2021

SUBJECT : Review of MSR#5 and MSR#6 on facial paralysis for the PFIZER-
OBJET BIONTEH COVID-19 Vaccine

- ☐ No Action Required—FYI Only
- ☒ Recommended For Immediate Action
- ☐ Recommended For Action Post Approval/at Next Opportunity

Memorandum

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The Bureau of Biologics, Radiopharmaceuticals and Self-Care Products (BBRS) of the Marketed Health Products Directorate (MHPD) reviewed the 5th and 6th Summary Monthly Safety Reports for the Pfizer-BioNTech COVID-19 Vaccine covering the months of April (April 01, 2021 to April 29, 2021) and May 2021 (April 30, 2021 to May 31, 2021) respectively. During these reporting periods the MAH discussed several safety topics, including but not limited to 16 Adverse Events of Special Interest (AESI).

Following the review of the data provided in the MSR#5¹ the MHPD did not agree with the MAH's assessment leading to closure of the signals on facial paralysis. Therefore, the MHPD requested in a letter sent to the MAH on June 07, 2021 a discussion regarding the need to submit a new *Post-Authorization change – PM safety update and/or update the risk management plan* regarding the risk of Facial paralysis /Bell's Palsy based on the imbalance observed in the clinical trials follow-up, increase in frequency of reporting from the post-market data, and safety information captured in other jurisdictions. Facial Paralysis and/or Bell's Palsy is labeled in the Clinical adverse reaction section of the EMA-SmPC and EUA USPI (including Bell's Palsy). The MHRA Pfizer Summary of Product Characteristics also includes acute peripheral facial paralysis as an ADR with a frequency of 1:1000.

The possible labelling of these events was discussed in a meeting with Pfizer Canada and BRDD on June 21, 2021.

Three additional serious cases of Bell's Palsy were reported in the MSR#6² submitted on June 15, 2021. Bell's Palsy is an AESI that is closely monitored in Canada by the PHAC and MHPD. Up to June 25, 2021, 145 cases of Bell's palsy were reported to the Canadian databases, including cases meeting the Brighton Collaboration criteria for diagnosis level 1 to 4. **Beginning of Confidential Information** Cases of Bell's Palsy following immunization with Pfizer BioNTech vaccine were statistically disproportionally reported in the Canadian databases as discussed in section 6 of this report. **End of Confidential Information.** [REDACTED]

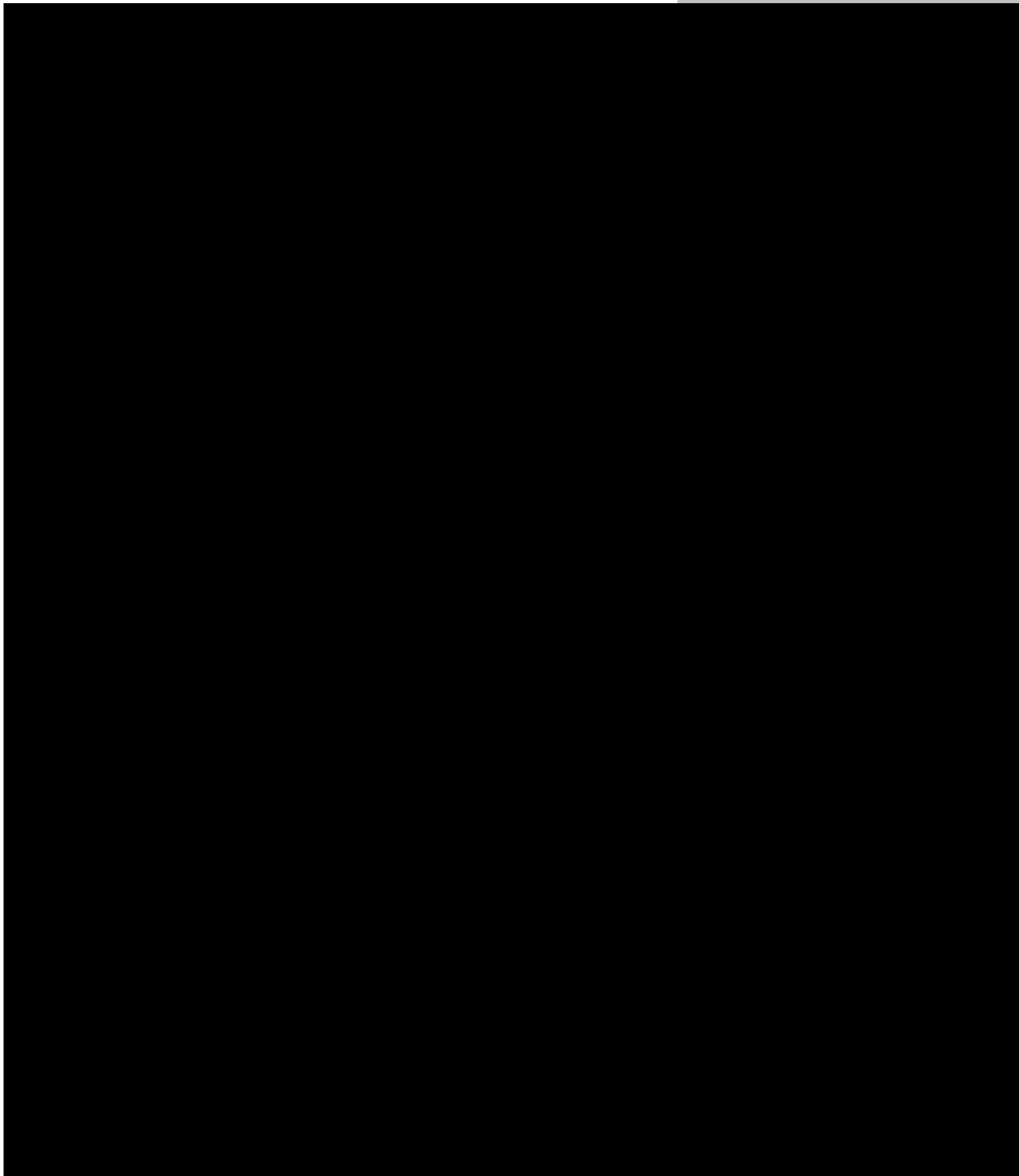
Overall, the MAH should be requested to submit a new Post-Authorization change – PM safety update the risk of facial paralysis/Bell's Palsy, based on the previous assessment showing an imbalance in Clinical trials, labelling in other jurisdictions and given that serious Canadian cases have been reported following immunization with the Pfizer BioNTech vaccine including cases corresponding to the Brighton Collaboration level 1 to 4.

¹ DSTS#251813, HC6-024-e243022 (1.0) Reg Info - Post Market Tracker

² DSTS#253419,) HC6-024-e243022 (253419 - Response to MHPD request dated 2021-06-07 (April 30 to May 31, 2021)) - Summary Monthly Safety Report 6 30-APR-2021 through 31-May-2021

Memorandum

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³ <https://www.gov.uk/government/publications/regulatory-approval-of-pfizer-biontech-vaccine-for-covid-19/information-for-healthcare-professionals-on-pfizerbiontech-covid-19-vaccine>

⁴ <https://www.fda.gov/media/144413/download>

⁵ https://www.ema.europa.eu/en/documents/product-information/comirnaty-epar-product-information_en.pdf

Memorandum

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Sent: 2021-07-07 6:07 PM
To: Hunt, Melissa (HC/SC)
Cc: Alhaddad, Saj (HC/SC); Rose, Jhona (HC/SC)
Subject: 253419_Pfizer BioNTech SMSR 6_2021-07-07_0.1.docx
Attachments: 253419_Pfizer BioNTech SMSR 6_2021-07-07_0.1.docx

Hi Melissa,

Please find attached the first draft of the Pfizer MSR 6 for your review.

I apologize for the delay.

Thank you,
Myriam

Marketed Health Products Directorate Direction des produits de santé commercialisés

PERIODIC BENEFIT-RISK EVALUATION REPORT (PBRER) REVIEW COMPREHENSIVE

PFIZER-BIONTECH COVID-19 VACCINE (BNT162B2, TOZINAMERAN)

SUMMARY MONTHLY SAFETY REPORT 6 29 APRIL 2021 TO 31 MAY 2021

CONTROL # 253419

(Including the MAH's Response to MHPD Requests under control number 253419)

Position Title: Director / Directeur(ice)
Bureau: Bureau of Biologics, Radiopharmaceuticals and Self-Care Products/ Bureau des produits biologiques, radiopharmaceutiques et auto-administratifs
Date: 07 July 2021
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EXECUTIVE SUMMARY

This Summary Monthly Safety Report 6 for the Pfizer-BioNTech COVID-19 Vaccine (BNT162B2, tozinameran) covers the period from 30 April 2021 to 31 May 2021.

Pfizer-BioNTech COVID-19 Vaccine (BNT162B2, tozinameran) is indicated for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS- CoV-2) in individuals 12 years of age and older.

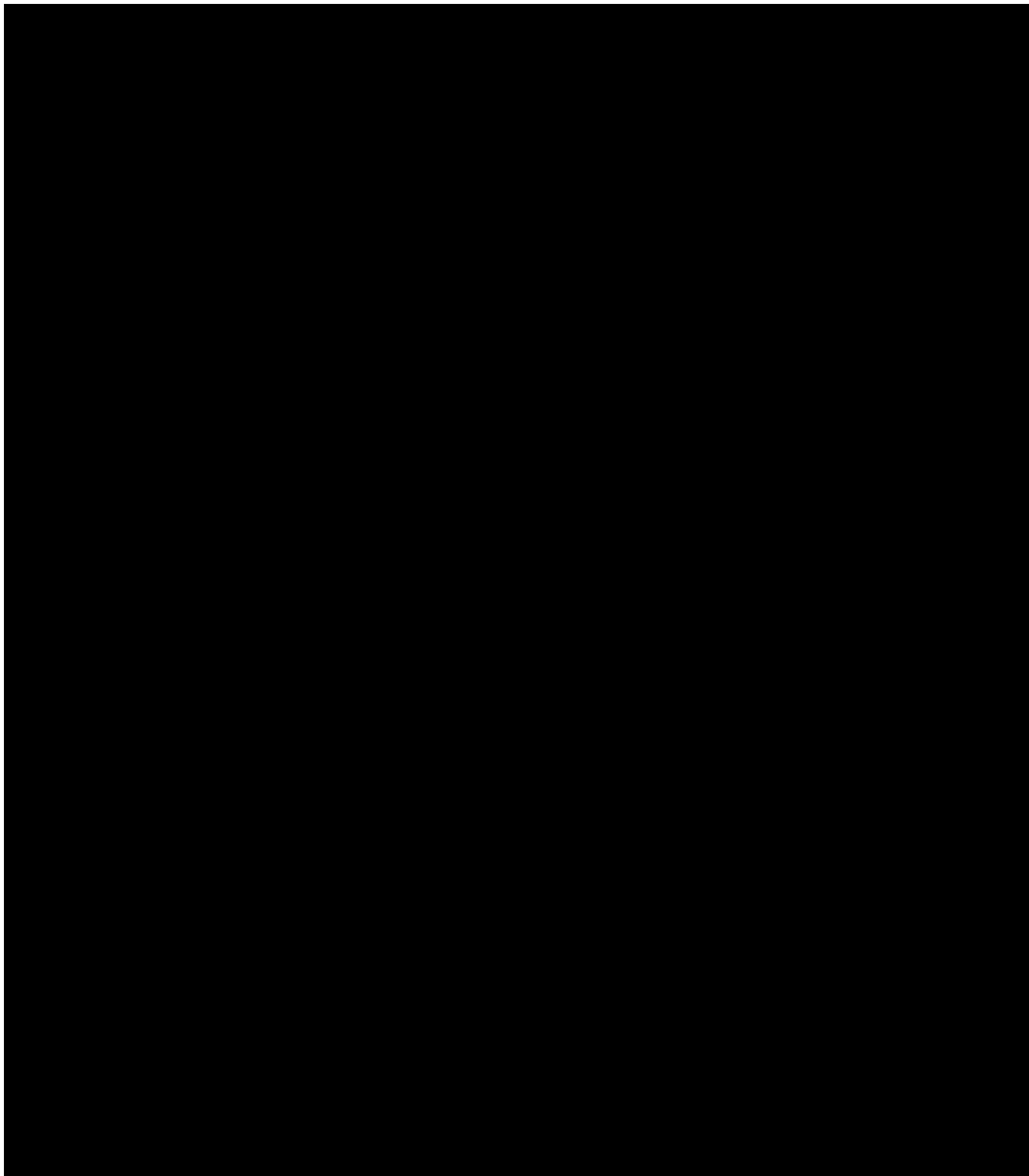
The Pfizer-BioNTech COVID-19 Vaccine (BNT162B2, tozinameran) received marketing authorization in Canada under the *Interim Order Respecting the Importation, Sale and Advertising of Drugs for Use in Relation to COVID-19* (control no. 244906; 09 December 2020). The interim authorization of the Pfizer-BioNTech COVID-19 Vaccine is subject to Terms and Conditions that need to be met by the MAH. The Pfizer-BioNTech COVID-19 Vaccine has received temporary authorisation for emergency supply in 35 countries and conditional marketing authorisation approval in 43 countries globally.

The scope of this review is to assess the Summary Monthly Safety Report (SMSR) #6 for Pfizer-BioNTech COVID-19 Vaccine and determine whether the Terms and Conditions relevant to adverse events reporting are met by the MAH and to follow-up on issues that have been identified by the MHPD during the previous reporting interval.

It was estimated that approximately 220,976,340 doses of the Pfizer-BioNTech COVID-19 Vaccine were shipped worldwide during the current reporting interval from 30 April 2021 to 31 May 2021. Of these, 10,452,780 doses were shipped to Canada. Of these, 8,884,863 were administered in Canada in the current interval.

A total of 47,174 cases with 174,446 adverse events were reported during this interval. Of the 47,174 cases

- a. 43 % of the reported cases were assessed as serious (20,288), 57% of the cases (26,885) were assessed as nonserious
- b. The majority of cases were from the United Kingdom (10,047) and the United States (8,975). Four hundred and twenty-three cases (423) were from Canada. One hundred and ninety (190) cases were in the previous interval period.
- c. Women represented the majority of the reported cases with 32,751 cases and men represented 11,506 cases (unknown data in 2,917 cases).
- d. The median age was 49.0 years old, with approximately a third of the cases 14,682 cases between the ages of 31 and 50 years old. Corresponding figure for age \leq 17 years old and age \geq 65 years old were 327 and 10,167, respectively (unknown age in 7,391 cases).
- e. Nine hundred and seventy-one (971) cases had a fatal outcome.



[REDACTED]

[REDACTED]

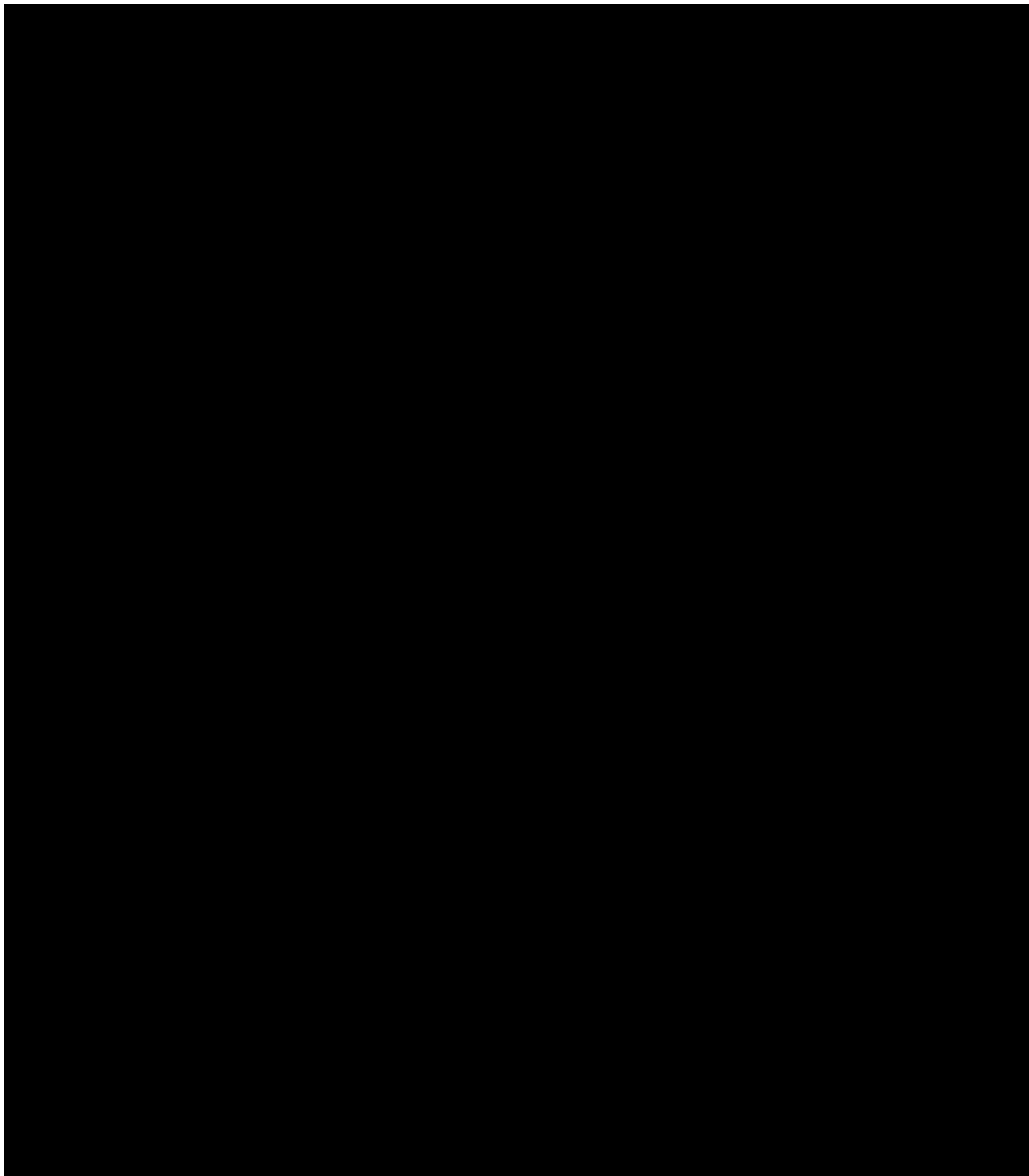


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1 INTRODUCTION

Control # / SAP #	253419
Canadian Market Authorization Holder (MAH) /Sponsor	Pfizer Canada ULC BioNTech Manufacturing GmbH
Product trade name	Pfizer-BioNTech COVID-19 vaccine
Active ingredient	BNT162B2, tozinameran
International Birth Date (IBD)	19 December 2020 (Switzerland)
Date Notice of Compliance (NOC) issued	09 December 2020
Date of marketing in Canada	14 December 2020
Type of document (PBRER, PSUR, ASR, PADERs, other)	Summary Monthly Safety Report
PBRER # and reporting interval	30 April 2021 to 31 May 2021
Last PBRER reviewed # and reporting interval	01 December 2020 to 31 December 2020 (control no. 248389) 01 January 2021 to 31 January 2021 (control no. 248783) 01 February 2021 to 28 February 2021 (control no. 250059) 01 March 2021 to 31 March 2021 (control no. 251805) 01 April 2021 to 29 April 2021 (control no. 251813)
Last RMP reviewed # and date	European RMP (EU RMP) version 2.0 (control no. 253040) Canadian addendum to the RMP dated May 2021
Date of current Canadian Product Monograph (CPM)	19 May 2021
Other documents submitted with the PBRER	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No Specify:
Foreign review available	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No Specify:
PBRER review type	Comprehensive

1.1 DESCRIPTION OF PRODUCT

BNT162b2 (or tozinameran) is a white to off-white frozen dispersion provided as concentrate for dispersion for injection (sterile concentrate) as multidose vial to be diluted before use. The multidose vial contains 6 doses of 0.3 mL after dilution if low dead-volume syringes and/or needles can be used to extract a 6th dose from a single vial. Each dose contains 30 micrograms of BNT162b2 as well as excipients.

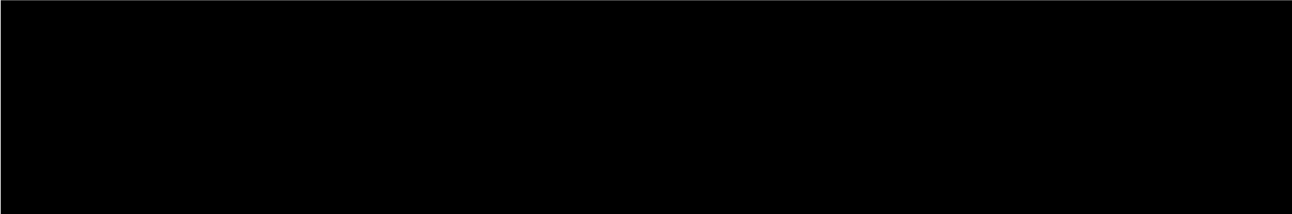
BNT162b2 is single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free *in vitro* transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2.

The nucleoside-modified mRNA is formulated in lipid nanoparticles, which enable delivery of the RNA into host cells to allow expression of the SARS-CoV-2 S antigen. The vaccine elicits both neutralizing antibody and cellular immune responses to the spike (S) antigen, which may contribute to protection against COVID-19.

1.2 PRODUCT USE

1.2a. Authorized indications in Canada

Pfizer-BioNTech COVID-19 Vaccine (COVID-19 mRNA Vaccine) is indicated for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS- CoV-2) in individuals 12 years of age and older.




1.2b. Additional indications/uses noted in the PBRER

There is no additional indication noted in the Summary Monthly Safety Report.

1.3 IS THERE A PRE-MARKET SUBMISSION CURRENTLY UNDER REVIEW FOR THIS PRODUCT?

☒ No ☐ Yes



2 TRIGGER AND SCOPE OF THIS REVIEW

On 09 December 2020, the Pfizer-BioNTech COVID-19 Vaccine (BNT162B2, tozinameran) received marketing authorization in Canada under the *Interim Order Respecting the Importation, Sale and Advertising of Drugs for Use in Relation to COVID-19* (control no. 244906). The interim authorization of the Pfizer-BioNTech COVID-19 Vaccine is subject to terms and conditions that need to be met by the MAH. The terms and conditions relevant to adverse events reporting include the following:

Pfizer Canada ULC is required to submit monthly safety reports for the period of the Interim Order authorization, unless otherwise determined by Health Canada. The monthly safety reports should be submitted within 15 days after the last day of a month, beginning after the first full calendar month after authorization. These reports should contain the following:

- Interval and cumulative number of reports (serious and non-serious), overall and by age groups and in special populations (e.g. pregnant women)
- Interval and cumulative number of reports per HLT and SOC
- Number of reports in Canada and Global
- Exposure data, stratified by country, age groups, race and ethnicity
- Changes to reference safety information in the interval
- Ongoing and closed signals in the interval
- List of adverse events of special interest including the Safety Platform for Emergency Vaccines list and RMP safety concerns (including the additional missing information): reports – numbers and relevant cases, including time-to-onset and O/E analyses
- Fatal reports – numbers and relevant cases, including observed/expected analyses
- Vaccination failure / lack of efficacy (including confirmed and suspected cases) and errors – number relevant cases
- Potential interaction with other vaccines/concomitant treatments-number and relevant cases
- Summary outcomes of some of the routine pharmacovigilance activities (as presented in the EU RMP Part III and applied in the Canadian context) should be included for the purpose of rapid signal detection and communication activities. Summary of all ongoing studies can be included in the first six-month scheduled PBRER, unless a safety signal is identified that requires immediate regulatory action.
- Risk/benefit considerations

The scope of this review is to assess the current Summary Monthly Safety Report (SMSR) for the Pfizer-BioNTech COVID-19 Vaccine and determine whether the MAH meets the terms and conditions relevant to adverse event reporting (as listed immediately above) and to follow-up on issues that the MHPD identified during the previous reporting interval.

3 ACTIONS TAKEN IN THE REPORTING INTERVAL FOR SAFETY REASONS

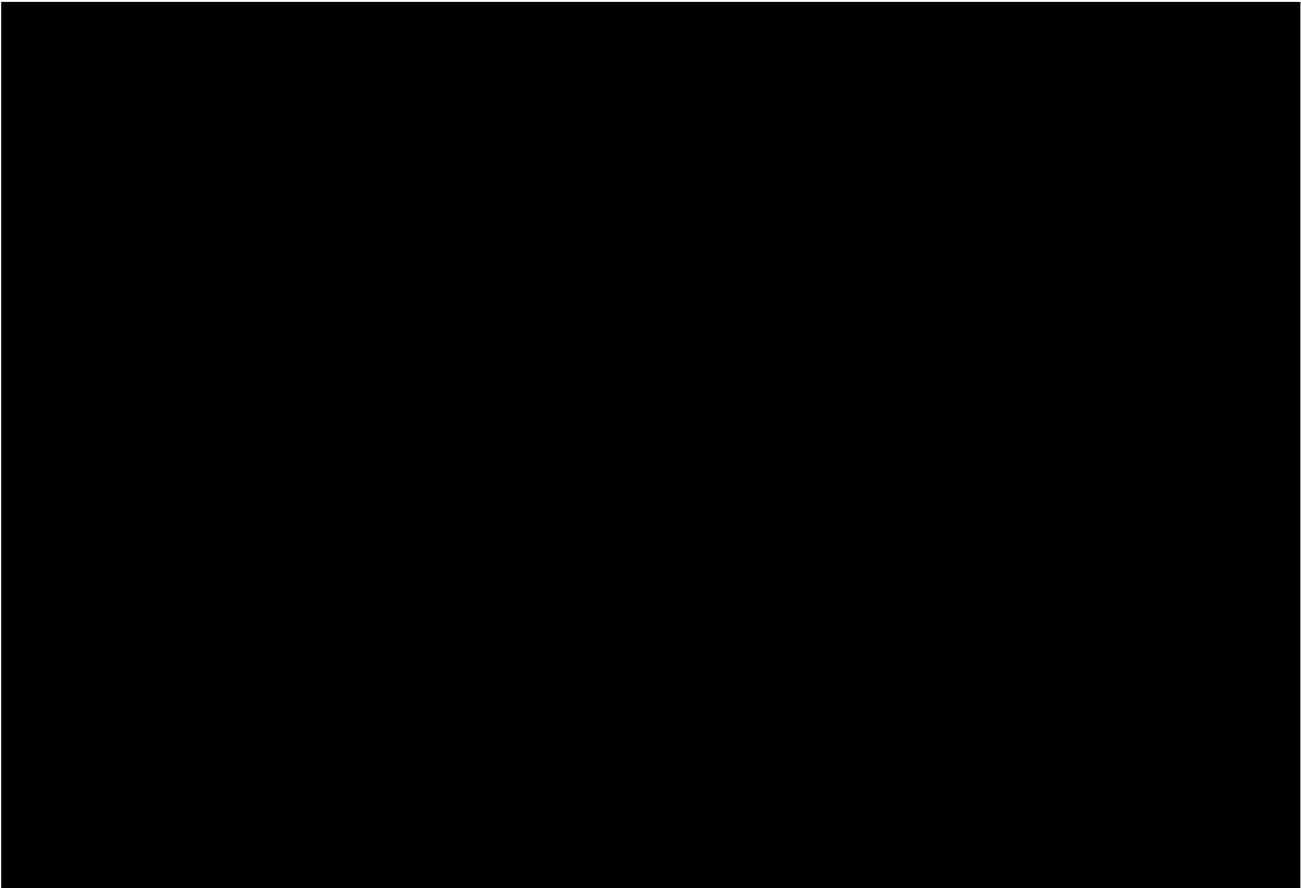
3.1 HAVE ACTIONS TAKEN FOR SAFETY REASONS BY THE MAH OR REGULATORY AUTHORITIES BEEN REPORTED?

☒ Yes ☐ No

Current interval:

No action was reported in the current interval.

Late Breaking information:



4 CHANGES TO THE REFERENCE SAFETY INFORMATION (RSI)

The RSI for this SMSR is the BNT162b2 Core Data Sheet (CDS) Version 4.0 dated 19 May 2021, in effect at the end of the reporting period.

The previous BNT162B2 CDS Version 3.0 dated 20 April 2021 was also in effect during the reporting period. The MAH updated the CDS version 3.0 on 19 May 2021 to include: Asthenia, Lethargy, Decreased appetite, Hyperhidrosis and Night sweats as adverse drug reactions in Section 4.8 Undesirable effects, and the addition of warning text for Vaccine stress-related responses (including Dizziness, Fainting, Palpitations, Increases in heart rate, Alterations in blood pressure, Feeling short of breath, Tingling sensations, Sweating and/or Anxiety) in Section 4.4 Special warnings and precautions for use.

5 ESTIMATED EXPOSURE AND USE PATTERNS

It is estimated that approximately 639,868,710 doses of the Pfizer-BioNTech COVID-19 Vaccine were shipped worldwide through 31 May 2021, corresponding to approximately 542,013,978 doses administered cumulatively. During the current reporting period (from 30 April 2021 through 31 May 2021) approximately 220,976,340 doses were shipped worldwide corresponding to approximately 188,860,682 doses administered.

In Canada, 20,120,880 doses were shipped cumulatively, corresponding to approximately 17,102, 748 doses administered including 8,884,863 doses administered during the reporting period compared to 3,309,696 doses administered in the previous interval.

6 DATA FROM PBRER SUMMARY TABULATIONS AND DATABASE SEARCHES

6.1 ADVERSE REACTION CODING DICTIONARY

The MedDRA version 24.0 was used to code adverse events/reactions during this reporting interval.

6.2 CUMULATIVE SUMMARY TABULATIONS OF SERIOUS ADVERSE EVENTS FROM CLINICAL TRIALS

Adverse events/reactions reported from clinical trials are discussed throughout this report.

6.3 CUMULATIVE AND INTERVAL SUMMARY TABULATIONS OF ADVERSE REACTIONS FROM POST-MARKETING DATA SOURCES

Cumulative number of cases from post-market experience (up to 31 May 2021):

The MAH received 167,956 reports from post-marketing data sources for Pfizer-BioNTech COVID-19 Vaccine through 31 May 2021. Of these, 1142 case reports were from Canada including 423 in the current interval.

Interval number of cases from post market experience (30 April 2021 up to 31 May 2021):

The MAH retrieved 47,174 cases (containing 174,446 events) in the current reporting interval. Of these, including 423 cases from Canada

MedDRA PTs reported in $\geq 2\%$ * Cases in the current interval/cumulative and relevant Canadian labelling

MedDRA SOC MedDRA PT	AEs (AERP%) (interval) N = 47174	AEs (AERP%) N = 167956	CPM Labelling (Y/N)
Blood and lymphatic system disorders			
Lymphadenopathy ^a	1914 (4.06%)	8382 (4.99%)	Y
Cardiac disorders			
Tachycardia	1093 (2.32%)	3596 (2.14%)	Y (partially labelled: fast heartbeat in the context of an allergic reaction, palpitations in the context of myocarditis)
Gastrointestinal disorders			
Nausea ^a	5053 (10.71%)	19303 (11.49%)	Y
Diarrhoea ^a	1786 (3.79%)	6879 (4.10%)	Y
Vomiting ^a	1664 (3.53%)	6253 (3.72%)	Y
General disorders and administration site conditions			
Fatigue ^a	7076 (15.00%)	28432 (16.93%)	Y
Pyrexia ^a	7341 (15.56%)	29507 (17.57%)	Y (fever)
Chills ^a	4990 (10.58%)	20176 (12.01%)	Y
Vaccination site pain ^a	4875 (10.33%)	18829 (11.21%)	Y
Pain ^a	2968 (6.29%)	12683 (7.55%)	Y
Malaise ^a	2968 (6.29%)	12683 (7.55%)	Y (feeling unwell)
Asthenia ^a	3460 (7.33%)	10855 (6.46%)	Y (weakness)
Drug ineffective ^b	1030 (2.18%)	4545 (2.71%)	
Feeling abnormal	4545 (2.71%)	3399 (2.02%)	Y (partial labelling: feeling unwell)
Immune system disorders			
Anaphylactic reaction ^a	758 (2.46%)	1965 (1.79%)	Y
Infections and infestations			
COVID-19 ^b	1898 (4.02%)	7063 (4.21%)	Y
Herpes Zoster	1243 (2.63%)	2234 (1.33%)	N

MedDRA SOC MedDRA PT	AEs (AERP%) (interval) N = 47174	AEs (AERP%) N = 167956	CPM Labelling (Y/N)
Musculoskeletal and connective tissue disorders			
Myalgia ^a	5531 (11.72%)	21315 (12.69%)	Y (muscle pain)
Pain in extremity ^a	4103 (8.70%)	15661 (9.32%)	Y
Arthralgia ^a	4282 (9.08%)	16204 (9.65%)	Y (joint pain)
Nervous system disorders			
Headache ^a	11689 (24.78%)	40612 (24.18%)	Y
Dizziness	4039 (8.56%)	13267 (7.90%)	Y
Paraesthesia	1366 (2.90%)	5337 (3.18%)	N (will be included in RSI)
Hypoaesthesia	1103 (2.34%)	3722 (2.22%)	N
Respiratory, thoracic and mediastinal disorders			
Dyspnoea ^c	1883 (3.90%)	7337 (4.37%)	Y (partially labelled: shortness of breath as part of the case definition of Covid-19)
Cough ^c	1413 (3.00%)	4434 (2.64%)	Y (partially labelled: shortness of breath as part of the case definition of Covid-19)
Oropharyngeal pain	1126 (2.39%)	3408 (2.03%)	N
Skin and subcutaneous tissue disorders			
Rash ^a	1791 (3.80%)	6121 (3.64%)	Y
Pruritus ^a	1949 (4.13%)	3845 (3.51%)	Y
Sensitive skin	1737 (3.68%)	2429 (1.45%)	N
Erythema ^a	1332 (2.82%)	4354 (2.59%)	Y (partially labelled: Redness/local reaction)
Urticaria	1002 (2.12%)	3275 (1.95%)	N
Total number of events	56829	223114	

6.4 CANADIAN ADVERSE REACTION DATA

6.4.1 Was a general search of the Canada Vigilance Database done?

☒ Yes ☐ No

6.4.2 If YES, indicate the Canada Vigilance reference #/date of online search, search strategy, results, and discuss the data

The Marketed Health Products Directorate (MHPD) performs daily Canada Vigilance searches for adverse reaction reports associated with Pfizer-BioNTech COVID-19 Vaccine. Adverse reaction reports are assessed independently by a scientific evaluator and a medical evaluator.

During the reporting interval of 01 April 2021 to 30 April 2021, 326 adverse reactions reports were recorded for the Pfizer-BioNTech. Of these adverse reactions, reports 7 were fatal. All these fatal reports were in patients aged 54, 58, 65 72, 72, 91, 91, 4 males, 1 female. Co-reported PTs include cerebral hemorrhage (2), pulmonary embolism, headache, myocardial infarction (2), cerebrovascular accident, and sudden death .



OTHER SAFETY DATABASES SEARCHES

The Canadian Adverse Events Following Immunization Surveillance System (CAEFISS) is a federal, provincial and territorial public health post-market vaccine safety surveillance system. CAEFISS is managed by the Public Health Agency of Canada (PHAC).

Up to and including 25 June 2021, 8570 adverse events following immunization (AEFIs) were reported to the Canada Vigilance Program and CAEFISS in Canada.¹ Of these 1884 were serious.

¹ <https://health-infobase.canada.ca/covid-19/vaccine-safety/>

Start of Confidential Information

Reports from the CAEFISS database up to July 05, 2021, as analyzed by the PHAC showing a statistical disproportional signal in all 5 statistical signal detection methods (included below):

AEFI's of interest (Pfizer/BioNTech COVID-19 vaccine)																			
Vaccination	AEFI	Pfizer Vaccine/AEFI events	Other vaccine/AEFI events	Proportional reporting ratio (PRR)	95% lower confidence interval (IC)	95% upper confidence interval (IC)	Chi-square statistic (P-Value)	Chi-square expected cell frequency of less than 10	Chi-square expected cell frequency of less than 5	Reporting Odds Ratio (IC)	Information Component (IC)	95% lower credibility interval (IC)	95% lower confidence interval (IC)	95% upper confidence interval (IC)	PAR signal detection flag	Chi-square signal detection flag	Chi-square signal detection flag (Yates correction)	IC signal detection flag	PAR signal detection flag
Pfizer/BioTech	Anaphylaxis	613	835	4.5726	4.1448	5.045	1043.94	54141	0	5.2330	1.6119	1.47763	1.70805	4.7372	5.914	1	1	1	1
Pfizer/BioTech	Anaphylaxis (Brighton Collaboration levels 1-3)	84	25	15.9452	10.0584	25.282	252.68	247.61	0	18.217	2.35178	1.91702	2.62965	10.1973	25.773	1	1	1	1
Pfizer/BioTech	Other allergic reactions	1322	7247	1.1362	1.0640	1.191	27.09	26.83	0	1.2195	1.5724	0.9946	2.2323	1.1280	1.205	1	0	0	1
Pfizer/BioTech	Seizure	127	131	6.0384	4.7425	7.888	273.77	270.78	0	6.2199	181677	1.52313	2.02897	4.8803	7.960	1	1	1	1
Pfizer/BioTech	Seizures	78	219	2.2184	1.7172	2.886	38.93	37.88	0	2.2450	91856	54123	1.18572	1.7295	2.914	1	1	1	1
Pfizer/BioTech	Anaesthesia	108	31	21.2377	14.2952	31.730	488.41	481.07	0	21.9043	2.45282	2.13123	2.88493	14.6570	32.735	1	1	1	1
Pfizer/BioTech	Parosynthesis	678	2184	1.9336	1.7871	2.092	261.57	260.64	0	2.1484	77529	64849	86740	1.9531	2.359	1	0	0	1
Pfizer/BioTech	Other neurological diagnosis	1080	4773	1.3833	1.3071	1.464	118.22	117.75	0	1.5339	39333	29193	46701	1.4240	1.665	1	0	0	1
Pfizer/BioTech	Arrhythmia	87	150	2.7821	2.0903	3.703	53.31	51.87	0	2.8154	1.14515	73988	1.43536	2.1083	3.783	1	1	1	1
Pfizer/BioTech	Thrombocytopenia	35	47	4.6383	2.9985	7.175	57.43	55.03	0	4.6735	152388	102036	1.94412	3.0129	7.249	1	1	1	1
Pfizer/BioTech	Vomiting	216	1072	1.2550	1.0885	1.448	3.79	3.54	0	1.2770	27698	05207	43993	1.0334	1.478	1	0	0	1
Pfizer/BioTech	Diarrhea	191	896	1.3277	1.1402	1.546	13.28	12.96	0	1.3458	34339	10477	51723	1.1485	1.580	1	0	0	1
Pfizer/BioTech	Platelet disorders	32	44	4.5235	2.8768	7.133	51.11	48.78	0	4.5681	1.55112	37147	1.37341	2.6888	7.201	1	1	1	1
Pfizer/BioTech	Transverse myelitis	7	14	3.1143	1.2578	7.711	6.70	5.17	1	3.1183	1.13981	1.13981	1.13981	1.2578	7.711	1	1	1	1
Pfizer/BioTech	Arteriovenous lymphatic stenosis	272	574	2.3005	1.9225	2.682	117.31	116.17	0	2.3006	96003	73300	1.10480	2.0254	2.788	1	1	1	1
Pfizer/BioTech	Embolic and thrombotic events	176	34	11.6620	9.1011	14.944	503.46	503.11	0	12.2017	2.22124	1.67189	2.40167	9.4750	15.713	1	1	1	1
Pfizer/BioTech	Cerebrovascular accident	30	13	14.3736	7.5046	27.530	113.04	108.33	1	14.4844	2.54175	1.67189	2.40167	9.4750	15.713	1	1	1	1
Pfizer/BioTech	Transient cerebrovascular events	13	3	26.9305	7.6950	54.671	61.04	55.51	1	27.0333	2.31477	1.37530	2.35786	7.7133	35.053	1	1	1	1
Pfizer/BioTech	Pulmonary embolism	53	6	55.0151	23.6688	127.834	266.50	260.45	1	55.0144	2.62576	2.17040	2.55360	23.9750	123.832	1	1	1	1
Pfizer/BioTech	Myocardial infarction	12	3	24.9143	7.0340	66.247	55.12	49.71	1	24.9331	2.27523	1.30053	2.34574	7.0494	66.611	1	1	1	1
Pfizer/BioTech	Coagulopathies and bleeding diatheses	15	50	1.6666	1.0505	3.324	4.67	3.93	1	1.8722	70747	1.16350	1.30066	1.0502	3.337	1	0	0	1
Pfizer/BioTech	Vascular haemorrhagic disorders	89	423	1.2822	1.0312	1.619	4.97	4.66	0	1.2395	31069	1.04043	55379	1.0314	1.637	1	0	0	1
Pfizer/BioTech	Cardiac failure	12	1	74.7430	3.7213	574.566	61.13	60.77	1	74.3660	2.44322	1.48458	3.1072	5.7471	576.880	1	1	1	1
Pfizer/BioTech	Myocarditis	45	21	13.3470	7.9605	22.379	163.95	159.41	1	13.5010	2.24020	1.74445	2.58437	8.0333	22.650	1	1	1	1
Pfizer/BioTech	Haemorrhage	4	4	6.2286	1.5584	24.894	8.78	6.01	1	6.2343	1.46561	1.46561	1.46561	1.5584	24.893	1	1	1	1
Pfizer/BioTech	Acute kidney injury	3	6	3.3423	3.3274	26.233	26.63	23.10	1	3.3535	1.65330	74434	2.54465	3.3300	26.322	1	1	1	1
Pfizer/BioTech	Chilblains	5	0	-	-	-	31.15	24.34	1	1	2.25641	64423	3.19101	-	-	0	0	0	1
Pfizer/BioTech	Cerebral ischaemias	22	42	4.7455	3.0001	7.507	53.04	51.40	0	4.7707	1.57103	1.02332	2.01615	3.0130	7.573	1	1	1	1
Pfizer/BioTech	Tinnitus	27	55	3.0577	1.9317	4.940	25.15	23.57	0	3.0730	1.51523	57134	1.65343	1.9352	4.077	1	1	1	1
Pfizer/BioTech	Sensorineural hearing loss	18	34	3.2375	1.8643	5.832	18.88	17.17	1	3.3089	1.26578	47341	1.81743	1.6688	5.665	1	1	1	1



End of Confidential Information

7 SIGNIFICANT FINDINGS FROM STUDIES OR OTHER SOURCES DURING THE REPORTING PERIOD

The SMSR did not include significant findings from completed and ongoing clinical trials, non-interventional studies, non-clinical data, and other periodic reports.

8 LATE-BREAKING INFORMATION

The section was not provided in this SMSR.

Actions taken for safety reasons by regulatory agencies

Based on data collected following mass immunization, the FDA, the MHRA and Health Canada requested a labelling update on June 25, 2021, to include a warning statement regarding the risk of myocarditis and/or pericarditis following immunization with mRNA COVID vaccines. The Pfizer BioNtech CPM was updated on 30 June 2021.

Following the review of the EU-RMP V2.0 and Canadian Addendum (DSTS# 253040) on June 07, 2021, the MAH was also requested to include myocarditis and pericarditis to the Canadian risk management plan and update the pharmacovigilance plan accordingly.

Start of Confidential Information

The EMA will be requesting a similar update as was done in other jurisdictions as well as an update in the RMP following the July 05-08, 2021 PRAC meeting.

End of Confidential Information

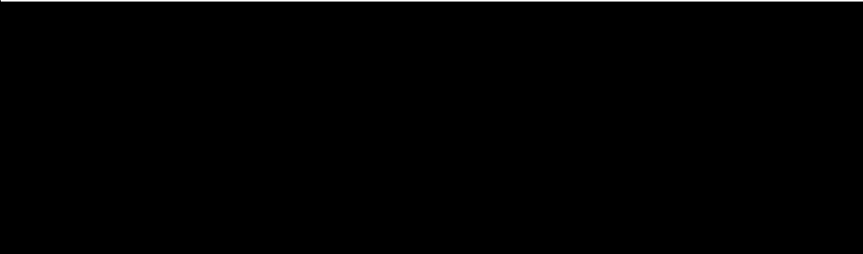
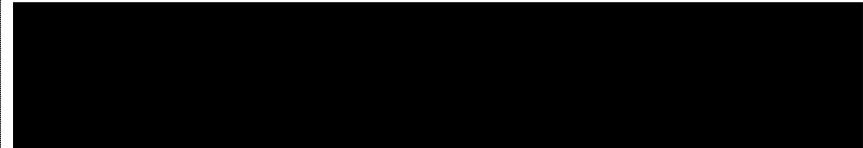
9 OVERVIEW OF SIGNALS DISCUSSED BY THE MAH: NEW, ONGOING, OR CLOSED

During the reporting period, 10 signals were evaluated by the MAH and closed during the reporting period:

Safety topic	Safety Trigger/ MAH's Assessment	MHPD comments
Appendicitis	Health Canada request/ Evidence does not support a causal association- Signal closed	

Dizziness	MHRA request/ The available information supports dizziness associated with the vaccination process (i.e. stress related response) but not a causal association with the vaccine itself at this time- Signal Closed	<p>From safety evaluation data reported under Appendix 3.7:</p> <p>Clinical trials</p> <p>The MAH notes that “Dizziness” was reported in 78 participants (0.4%) in the BNT162b2 group compared with 60 participants in the placebo group (AEs reported from Dose 1 to 1 month post dose 2 during the blinded controlled follow up period). Postural dizziness was reported by 2 (0.0%) BNT162b2 recipients and 1 (0.0%) placebo recipient.</p> <p>Post market cases (up to 30 April 2021) using MedDRA PT Dizziness</p> <p>f. A total of 15,260 cases were reported for BNT162b2.</p> <p>g. Median Age was 46. Most frequent reported age was between 31-50 years old</p> <p>h. Approximately 40% of the cases occurred within the first 24 hours. Co-reported events were most commonly reactogenicity events. The most common were headache (2718), nausea (2097), asthenia (1216), and chills (1130)</p> <p>i. There were 8 events of dizziness with a fatal outcome. 4 cases with a latency of Day 0. Of these, 3 cases were in patients between 80-94 years of age with a medical history of neurological and cardiac manifestations), 1 case with a fatal outcome with latency of Day 2, a 27 year-old male experienced dizziness and vomiting blood 2 days after vaccination.</p> <p>As per the Summary of the MAH’s assessment/conclusion: because dizziness is a term commonly used by patients to describe symptoms that are inconsistently defined, and based on the postauthorization reports, it is plausible that the dizziness experienced soon after vaccination is a potential manifestation of vaccination-related situational stress, anxiety and/or is confounded by the systemic reactogenicity experienced in the same time period. Cases of dizziness that described an inability to drive were relatively rare (11). Additionally, in the course of the Phase 2/3 clinical trials, events of dizziness were not meaningfully different in the active cohort (0.4%) compared to placebo cohort (0.3%).</p> <div></div>
Myocarditis/ pericarditis	Signal ongoing	The MAH retrieved 495 reports of myocarditis and pericarditis (up to May 25, 2021). Of the 495, there were 260 cases of myocarditis (all assessed as serious), 73 met a certainty in diagnosis of myocarditis when assessed based

	<p>on the Brighton's Collaboration (BC) diagnostic certainty criteria. 18 cases Eighteen (18) cases were classified as BC Level 1 (confirmed), 24 cases as BC level 2 (probable), 31 cases as BC level 3 (possible).</p> <p>The majority of the confirmed, probable and possible myocarditis case reports were in younger age groups below 39 years of age (48/73; 66%). None had a fatal outcome. There were more males than females. 2 cases assessed as possible myocarditis were from Canada.</p> <p>MAH's assessment/conclusion: The rate at which these events are reported (even without applying the diagnostic certainty criteria) do not exceed the expected background rate. It should be noted that with the case information currently available, only 18 (6.9%) of the cases could be assessed as "confirmed cases" of myocarditis as per Brighton Collaboration criteria. It is worth noting that the incidence rate of myocarditis in COVID-19 infected patients is 2.3 out of 100 in a recovering population. 5 Given the totality of the data, a causal association between the vaccine and myocarditis or pericarditis cannot be established. The MAH will continue to perform robust pharmacovigilance, follow up, and monitoring of this topic.</p> <div></div>
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Safety topic	Safety Trigger/ MAH's Assessment	MHPD comments
Abnormal behaviour/mental disorder	Japan PMDA/No validated signal	<p>The MAH did not provide the assessment regarding abnormal behaviour in the monthly safety report #6; however, the MAH concluded that the available data do not support this topic as a validated signal.</p> 
Acquired Hemophilia	Request from France ANSM/No Validated Signal	<p>The MAH did not provide the assessment regarding acquired hemophilia in the monthly safety report #6; however, the MAH concluded that the available data do not support this topic as a validated signal. The MAH noted that the ANSM 15th PV report of AEs found 3 cases of acquired hemophilia since the start of vaccination and considered it as a potential signal. A review of the small number of post-authorization AE reports of acquired hemophilia was undertaken and this topic was determined not to be a validated signal.</p> 
Acute disseminated Encephalomyelitis (ADEM)	PRAC request/No Validated Signal	<p>The MAH notes that ADEM has been described most frequently following measles mumps and rubella vaccinations, but at a lower incidence of ADEM after a wild-type measles encephalitis. Other reports of ADEM have been described both after H1N1 infection and H1N1 vaccination.</p> <p>Post-marketing cases</p>

		<p>-78 cases were reported including one case from a Pfizer-sponsored interventional study.</p> <p>-majority of cases (64/78) were medically confirmed.</p> <p>-Median reported age 51.5, mean 54.2 years</p> <p>- Of the 78 reports, 48 (61.5%) were reported as females, 29 (37.2%) as males, and in 1 (1.3%) case sex was not reported</p> <p>-Most cases were from the US (18) and UK (14), France and Spain (6 each)</p> <p>-Time to onset (reported in 58 cases) ranged between 2 to 21 days in 43 cases. 12 cases reported time to onset as the same vaccination day or day after. In 3 cases time to onset was reported as 22, 28 and 38 days post-vaccination.</p> <p>- Case outcome was reported as recovered/recovering/recovered with sequelae in 33 cases (42.3%), not recovered at time of reporting in 28 cases (35.9 %), and outcome was unknown in 11 cases (14.1%) .There were also 6 fatal cases (7.7%).</p> <p>-All cases were assessed according to BC criteria. None of the cases met BC level 1. 75 cases were assessed as follows:</p> <ul style="list-style-type: none">• 7 cases (9.2%) met level 2;• 11 cases (14.5%) met level 3;• 41 cases (55.3%) met level 4 (reported encephalitis/ADEM with insufficient evidence to meet the case definition);• 16 cases (21%) met level 5 (not a case of encephalitis/ADEM) <p>Among the 59 cases that met BC level 2,3 4, alternative explanations including previous disease/neurologic co-morbidities were reported.</p> <p>Of note, the MAH revised the observed to expected ratio based on a background rate of 5.3 per 100,000 person years to better align with the spontaneously reported case definition. In the previous SMR the MAH used a background rate of 0.1 from the ACCESS initiative.</p> <p>According to the MAH, given the totality of the available information, this review of the data did not support validation of a signal. Changes in the risk minimization measures or updates to the product information label are not warranted at this time. The benefit risk profile of the vaccine remains favorable. The topic will continue to be closely monitored.</p> <div></div>
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Safety topic	Safety Trigger/ MAH's Assessment	MHPD comments
Acute pancreatitis	Request from France ANSM/ No Validated Signal	<p>The MAH did not provide the assessment regarding acute pancreatitis in the monthly safety report #6; however, the MAH concluded that the available data do not support this topic as a validated signal. The MAH noted that the ANSM 14th PV report of AEs found 19 cases of acute pancreatitis since the start of vaccination and considered it as a potential signal. A review of the AE reports of acute pancreatitis was undertaken and this topic was determined not to be a validated signal.</p> <div></div>

Safety topic	Safety Trigger/ MAH's Assessment	MHPD comments
Guillain-Barre Syndrome	Request from France ANSM/No Validated Signal	<p>Post market cases</p> <p>The MAH retrieved 147 cases were from the database (up to May 10, 2021):</p> <ul style="list-style-type: none"> -76 females and 67 males -Age range between 18 to 97 years, mean 59.3 years - Most of the cases were reported from US (36, 24.5%), United Kingdom (30, 20.4%) followed by Japan (12, 8.2%). -The outcome of the event was reported as not recovered at time of reporting in 53 cases (36.1%), as recovering/resolving in 53 cases (36.0 %), and as unknown in 36 cases (24.5%) and fatal in 5 cases (3.4%) - Time to onset ranged from same vaccination day to 63 days following vaccination, with the majority of cases reported within 7 days of vaccination. <p>All cases have been assessed according to BC criteria as follows:</p> <ul style="list-style-type: none"> • 4 case (2.7 %) met level 1 • 16 cases (10.8 %) met level 2 • 1 case (0.7 %) met level 3 • 116 cases (79 %) met level 4 • 9 cases (6.1 %) met level 5 • 1 case (0.7%) was referring to another vaccine <p>Medical history found confounding factors in 33 cases (cerebrovascular accident (2), Chronic inflammatory demyelinating polyradiculoneuropathy (4), autoimmune disease, HIV and Cancer (14), Covid-19 infection (3 cases), symptoms in 1 case were pre-existing vaccination.</p> <p>MAH's assessment/conclusion: Most reported cases (79%) met level 4 of BC. Most cases meeting BC level 1 or 2 were confounded by preceding infection, implausible time to onset, symptoms pre-existing vaccination or GBS in the context of cerebral infarct. The upper limit of the 95% confidence interval for the observed to expected ratio did not exceed 1; therefore, a signal was not identified. Overall, given the totality of the available information, GBS is not considered to be a validated signal, changes in the risk minimization measures or updates to the product information label are not warranted at this time. The benefit risk profile of the vaccine remains favorable.</p>

Safety topic	Safety Trigger/ MAH's Assessment	MHPD comments
Menstrual cycle abnormalities	Request from Israel Ministry of Health/ No Validated Signal	<p>The MAH noted a review of menstrual terms from the clinical study data and from the postauthorization AE reports was undertaken. The available data did not support a validated signal.</p> <div></div>

Safety topic	Safety Trigger/ MAH's Assessment	MHPD comments
Transverse myelitis	Request from Australia TGA/ No validated signal	<p>The MAH noted several case reports describing transverse myelitis in temporal relationship with Corona virus infection have been published. The reported time to onset was between 8 days to 3 weeks upon infection symptoms.</p> <p><u>Post-market (data as of 17 May, 2021)</u></p> <ul style="list-style-type: none"> -67 cases identified. All cases were assessed as serious. -51 females, 15 males, and in one case gender was not reported. -Age range between 21 to 84 years (mean 48, median 43) -Most of the cases were reported from UK (23, 34.3%), followed by United States (20, 29.9%). -The outcome of the event was reported as not recovered at time of reporting in 30 cases (44.8%) resolving/recovering in 25 (37.3%) and unknown in 15 cases (17.9%).. All cases have been assessed according to BC criteria as follows: <ul style="list-style-type: none"> • 0 cases (0%) met level 1 • 2 cases (3%) met level 2 • 5 cases (7.5%) met level 3 • 53 cases (79.1%) met level 4 • 7 cases (10.4%) met level 5 - Time to onset was reported for 34 cases and ranged from the same vaccination day to 21 days after vaccination. - Unadjusted observed to expected ratio (O/E) analyses were conducted for the 67 reported TM cases. The O/E ratio was above 1 for the 21-day risk window and below 1 for the no risk window, indicating there may be an increased risk of TM among recipients of the BNT162b2 vaccine. <p>MAH's conclusion/assessment: The E/O analysis showed a small increase over the 21 days risk window nevertheless, as described in the O/E analysis the 21-day risk window is particularly conservative as all observed cases are included in the numerator of the O/E ratio regardless of the days since vaccination dose, which will lead to an overestimation of the ratio if observed cases occurred outside of the risk window. In addition, the ACCESS background rate used to calculate the expected number of cases is derived from medical records coded as transverse myelitis or a cute transverse myelitis while the observed cases were identified in the spontaneous reporting system using a broader search criteria (as specified in the method). Updates to the product information label is not warranted at this time.</p>

10 REVIEW OF NEW SAFETY INFORMATION

10.1 SUMMARY OF SAFETY CONCERNS

The summary of safety concerns for the Pfizer-BioNTech COVID-19 Vaccine can be found below. This summary includes ongoing safety concerns from both the European RMP (EU RMP) version 1.1 dated 15 April 2021, the US Pharmacovigilance Plan (PVP) version 0.4 dated 08 April 2021 and the South Africa RMP version 1.0 dated 24 March 2021.

Important identified risk	Anaphylaxis
Important potential risk	Vaccine-Associated Enhanced Disease (VAED), including Vaccine-Associated Enhanced Respiratory Disease (VAERD)
Missing information	Use in pregnancy and while breast feeding
	Use in immunocompromised patients
	Use in frail patients with co-morbidities (e.g., COPD, diabetes, chronic neurological disease, cardiovascular disorders, active tuberculosis)
	Use in patients with autoimmune or inflammatory disorders
	Interaction with other vaccines
	Long-term safety data
	Use in paediatric individuals <12 years of age
	Vaccine effectiveness



10.2 SUMMARY OF ADVERSE EVENTS OF SPECIAL INTEREST

The search criteria for the adverse events of special interest (AESIs) for the Pfizer-BioNTech COVID-19 Vaccine can be found in Appendix **Error! Reference source not found.** The list of AESIs takes into consideration AESIs from expert groups and regulatory authorities, including the Brighton Collaboration.

10.2.1 Adverse events of special interest (AESI)

Pfizer provided cumulative assessment for AESI(s) noted in the table below, and did not validate any signals or identify new risks emerging from their analysis. No further action was proposed, standard surveillance is applied.

AESI Category	MAH's assessment	MHPD comments
Anaphylactic Reactions <i>Search criteria:</i> <i>Anaphylactic reaction SMQ (Narrow and Broad, with the algorithm applied), selecting relevant cases according to BC criteria</i>	No signal	Anaphylaxis is labelled in the CPM under Warnings and Precautions. No new safety information based on the provided information, no further regulatory action is recommended at this time.


<p>Cardiovascular AESIs <i>Search criteria: PTs Acute myocardial infarction; Arrhythmia; Cardiac failure; Cardiac failure acute; Cardiogenic shock; Coronary artery disease; Myocardial infarction; Postural orthostatic tachycardia syndrome; Stress cardiomyopathy; Tachycardia</i></p>	<p>No signal</p>	<p>Number of cases: 1585 (3.4 % of the total PM dataset, compared to 2.8% in the previous reporting period) 1217 medically confirmed and 368 are non-medically confirmed; - age (n = 1502): ranged from 16 to 101 years (mean = 50.8 years, median = 46 years); -Subjects' age group (n = 1514): Adult36 (1088), Elderly (422) and Adolescent (4); -Reported relevant PTs: Tachycardia (1093), Arrhythmia* (177), Myocardial infarction* (170), Cardiac failure* (87), Acute myocardial infarction* (66), Cardiac failure acute* and Cardiogenic shock* (13 each), Coronary artery disease* and Postural orthostatic tachycardia syndrome* (10 each), Stress cardiomyopathy* (6). - Outcome:39 resolved/resolving (727), not resolved (182), fatal (119), resolved with sequelae (22) and unknown (596); -Median time to onset is 24 hours following vaccination.</p> <p>MAH's conclusion/assessment: No cardiovascular signals have emerged from the review of post-authorisation data. The review of cases and O/E analysis do not raise new concerns. Safety surveillance will continue.</p> <div></div>
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AESI Category	MAH's assessment	MHPD comments
COVID-19 AESIs <i>Search criteria: Covid-19 SMQ (Narrow and Broad) OR PTs Ageusia; Anosmia</i>	No signal	No new safety information based on the provided information, no further regulatory action is recommended at this time.
Dermatological AESIs <i>Search criteria: PT Chillblains; Erythema multiforme</i>	No signal	No new safety information based on the provided information, no further regulatory action is recommended at this time. There are currently a total of <u>11 cases</u> reported following the Pfizer BioNtech vaccine in the Canadian databses Chillbains and Erythema multiform are closely monitored by the MHPD and PHAC and are included in the AESIs for COVID vaccines.

AESI Category	MAH's assessment	MHPD comments
<p>Facial Paralysis <i>Search criteria: PTs Facial paralysis, Facial paresis, Oculofacial paralysis</i></p>	<p>No signal</p>	

² https://www.ema.europa.eu/en/documents/product-information/comirnaty-epar-product-information_en.pdf

³ <https://www.fda.gov/media/144413/download>

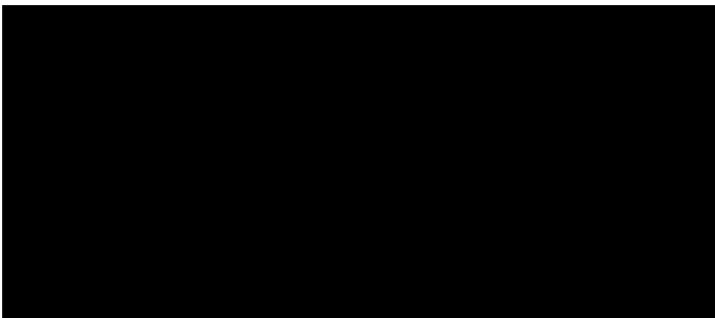
AESI Category	MAH's assessment	MHPD comments
<p>Haematological AESIs <i>Search criteria:</i> <i>Leukopenias NEC (HLT)</i> <i>OR Neutropenias (HLT)</i> <i>OR PTs Immune thrombocytopenia,</i> <i>Thrombocytopenia OR</i> <i>SMQ Haemorrhage terms</i> <i>(excl laboratory terms)</i></p>	No signal	<p>Most frequently reported relevant PTs (10 occurrences) include: Heavy menstrual bleeding (323), Contusion (227), Epistaxis (196), Thrombocytopenia* (186), Haemorrhage* (121), Vaginal haemorrhage (104), Vaccination site bruising (73), Petechiae (70), Intermenstrual bleeding (68), Immune thrombocytopenia* (57), Vaccination site haematoma (52), Haematoma (51), Purpura (46), Haematochezia (42), Vaccination site haemorrhage (41), Eye haemorrhage, Postmenopausal haemorrhage and Rectal haemorrhage (34 each), Conjunctival haemorrhage and Haematuria (27 each), Blood urine present (24), Ecchymosis, Haemoptysis and Internal haemorrhage (22 each), Gingival bleeding (21), Neutropenia (18), Gastrointestinal haemorrhage (15), Lymphopenia (14), Diarrhoea haemorrhagic, Haematemesis and Haemorrhage subcutaneous (13 each) and Blood blister, Leukopenia and Subdural haematoma (12 each)</p> 
<p>Musculoskeletal AESIs <i>Search criteria: PTs</i> <i>Arthralgia; Arthritis;</i> <i>Arthritis bacterial;</i> <i>Chronic fatigue syndrome; Polyarthritis;</i> <i>Post viral fatigue syndrome; Rheumatoid arthritis</i></p>	No signal	No new safety information based on the provided information, no further regulatory action is required at this time.

AESI Category	MAH's assessment	MHPD comments
Neurological AESIs (including demyelination) <i>Search criteria: Convulsions (SMQ) (Broad and Narrow) OR Demyelination (SMQ) (Broad and Narrow) OR PTs Ataxia; Cataplexy; Encephalopathy; Fibromyalgia; Intracranial</i>	No signal	<p>Most frequently reported relevant PTs (≥ 5 occurrences) included: Seizure* (236), Neuropathy peripheral* (101), Epilepsy (84), Guillain-Barre syndrome* (60), Generalised tonic-clonic seizure* (38), Fibromyalgia* (30), Febrile convulsion* and Multiple sclerosis* (23 each), Trigeminal neuralgia (22), Status epilepticus (16), Optic neuritis* (15), Multiple sclerosis relapse* (13), Ataxia (12), Myelitis transverse* (11), Tongue biting (8), Polyneuropathy (7), Acute disseminated encephalomyelitis*, Aura, Meningitis*, Meningitis aseptic*, Partial seizures*, Seizure like phenomena (6 each), Clonic convulsion, Intracranial pressure increased and Petit mal epilepsy (5 each);</p> <p>6 serious cases were reported in Canada in the current interval.</p>
Hepatic AESIs <i>Search criteria: Liver related investigations, signs and symptoms (SMQ) (Narrow and Broad) OR PT Liver injury</i>	No signal	<p>No new safety information based on the provided information, no further regulatory action is recommended at this time.</p>
Immune-Mediated/Autoimmune AESIs <i>Search criteria: Immune mediated/autoimmune disorders (SMQ) (Broad and Narrow) OR Autoimmune disorders HLGT OR PTs Cytokine release syndrome; Cytokine storm; Hypersensitivity</i>	No signal	<p>No new safety information based on the provided information, no further regulatory action is recommended at this time.</p>

<p>Pregnancy Related AESIs</p> <p><i>Search criteria: PTs Amniotic cavity infection; Caesarean section; Congenital anomaly; Death neonatal; Eclampsia; Foetal distress syndrome; Low birth weight baby; Maternal exposure during pregnancy; Placenta praevia; Pre-eclampsia; Premature labour; Stillbirth; Uterine rupture; Vasa praevia</i></p>	<p>No signal</p>	<p>The MAH provided a cumulative analysis regarding the outcome of reported pregnancies.</p> <p>Cumulatively a total of 995 unique pregnancies were reported, 317 of which were received during the reporting interval.</p> <p>Overall, the majority (763) of these cases had insufficient information to conduct a meaningful medical assessment of causality (eg, concomitant medications, trimester of exposure, pregnancy outcome, medical history). Of the 1036 cases reported cumulatively, 478 were assessed as serious. The most frequently reported pregnancy related events in these cases coded to the PTs Abortion spontaneous (187), Abortion missed (19), Foetal death (16), Premature baby (13), Foetal growth restriction (10), and Abortion (6).</p> <p>MAH’s conclusion: The review of the cases indicative of drug exposure during pregnancy did not reveal any new safety information.</p> <p>The MAH is conducting a post-authorization study (C4591015) to study the safety of the vaccine in pregnancy.</p> <div></div>
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AESI Category	MAH's assessment	MHPD comments
Renal AESIs <i>Search criteria: PTs Acute kidney injury; Renal failure.</i>	No signal	No new safety information based on the provided information, no further regulatory action is recommended at this time.
Respiratory AESIs <i>Search criteria: Lower respiratory tract infections NEC (HLT) OR Respiratory failures (excl neonatal) (HLT) OR Viral lower respiratory tract infections (HLT) OR PTs: Acute respiratory distress syndrome; Endotracheal intubation; Hypoxia; Pulmonary haemorrhage; Respiratory disorder; Severe acute respiratory syndrome</i>	No signal	No new safety information based on the provided information, no further regulatory action is recommended at this time.

AESI Category	MAH's assessment	MHPD comments
<p>Thromboembolic Events</p> <p><i>Search criteria:</i> <i>Embolism and thrombosis (HLGT), excluding PTs reviewed as Stroke AESIs, OR PTs Deep vein thrombosis; Disseminated intravascular coagulation; Embolism; Embolism venous; Pulmonary embolism</i></p>	<p>No signal</p>	<p>Most frequently reported relevant PTs (≥5 occurrences) included: Pulmonary embolism* (588), Deep vein thrombosis* (442), Thrombosis (339), Thrombophlebitis superficial (65), Thrombophlebitis (53), Venous thrombosis limb (37), Embolism(36), Pulmonary thrombosis (35), Venous thrombosis (24), Retinal vein occlusion (21), Retinal artery occlusion and Portal vein thrombosis (17 each), Mesenteric vein thrombosis (14), Retinal vein thrombosis (13), Jugular vein thrombosis and Peripheral artery thrombosis (11 each), Pelvic venous thrombosis (10), Arterial thrombosis, Intracardiac thrombus, Ophthalmic vein thrombosis and Subclavian vein thrombosis (8 each), Coronary artery thrombosis (7), Embolism venous and Pulmonary artery thrombosis (6), Retinal artery thrombosis (5);</p> <p>There were 23 cases of thromembolic events reported in the current interval in Canada</p> <div></div>

AESI Category	MAH's assessment	MHPD comments
Stroke <i>Search criteria: HLT Central nervous system haemorrhages and cerebrovascular accidents (Primary Path) OR HLT Cerebrovascular venous and sinus thrombosis (Primary Path)</i>	No signal	<p>Most frequently reported relevant PTs (≥ 5 occurrences) included:</p> <ul style="list-style-type: none"> o PTs indicative of Ischaemic stroke: Cerebrovascular accident* (308), Ischaemic stroke* (144), Cerebral infarction* (106), Cerebral venous sinus thrombosis* (35), Cerebral thrombosis* (22), Cerebral ischaemia (18), Embolic stroke (14), Thrombotic stroke* (9), Cerebral artery embolism, Cerebral venous thrombosis and Ischaemic cerebral infarction (8 each), Brain stem infarction and Cerebral artery occlusion (6 each) and Carotid artery occlusion, Carotid artery thrombosis, Cerebellar stroke, Cerebral artery thrombosis and Lacunar infarction (5 each); o PTs indicative of Haemorrhagic stroke: Cerebral haemorrhage* (93), Subarachnoid haemorrhage* (32), Haemorrhagic stroke* (18), Cerebral haematoma*, Haemorrhage intracranial* and Haemorrhagic transformation stroke (6 each); <p>8 cases were reported in Canada in the current interval.</p> 
Vasculitic Events <i>Search criteria: Vasculitides HLT</i>	No signal	No new safety information based on the provided information, no further regulatory action is required at this time.

10.3 SUMMARY OF SPECIAL SITUATIONS

10.3.1 Special situations

Overall, the MAH did not identify new safety signal from the evaluation of special situations (Death, Lack of Efficacy and Vaccine Interactions). : Causes of death most frequently reported (>2% of total fatal cases): Death (198), COVID-19 (76), Cardiac arrest (72), Sudden death (63), Dyspnoea (58), Pulmonary embolism (56), Cardio-respiratory arrest (49), Myocardial infarction (45), Vaccination failure (41), Pyrexia (39), COVID-19 pneumonia (35), Respiratory failure (34), Cerebrovascular accident, Drug ineffective (31 each), Cerebral haemorrhage, Pneumonia (29 each), Cardiac failure (23), and Vomiting (20).

11 EFFECTIVENESS STUDIES

As noted by the MAH, a statistically greater response was achieved in Study 2 in the adolescents 12 to 15 years of age compared to participants 16 to 25 years of age to demonstrate a non-inferior immune responses:

The geometric mean titers (GMT) ratio of the adolescents 12 to 15 years of age group to the participants 16 to 25 years of age group was 1.76, with a 2-sided 95% CI of 1.47 to 2.10, meeting the 1.5-fold non-inferiority criterion (the lower bound of the 2-sided 95% CI for the geometric mean ratio [GMR] >0.67) which indicates a statistically greater response in the adolescents 12 to 15 years of age than that of participants 16 to 25 years of age.

12 OTHER SAFETY CONCERNS AND FOLLOW-UPS

11.1. Responses to MHPD following the assessment of the April monthly safety report

In accordance with the Risk Management Plan Terms and Conditions, imposed under the Interim Order Respecting the Importation, Sale and Advertising of Drugs for Use in Relation to Covid-19, Pfizer Canada ULC is required to submit monthly safety reports for the period of the Interim Order authorization. As such, you are requested to submit the monthly safety report for the period of April 30, 2021 to May 31, 2021 including cumulative number of reports (serious and non-serious) and adverse events that occurred in Canada and globally for the Pfizer-BioNTech COVID-19 Vaccine (tozinameran) known to Pfizer Canada ULC and BioNTech Manufacturing GmbH. Actions for Pfizer Canada ULC and BioNTech Manufacturing GmbH stemming from the SMSR #5 review are to:

Comment 1

Discuss the need to submit a new Post-Authorization change – PM safety update and/or update the risk management plan regarding the following risks:

Facial paralysis /Bell's Palsy in association with the Pfizer-BioNTech COVID-19 Vaccine, based on the imbalance observed in the clinical trials, increase in frequency of reporting from the post-market data, and safety information captured in the EMASmPC and EUA USPI (including Bell's Palsy).

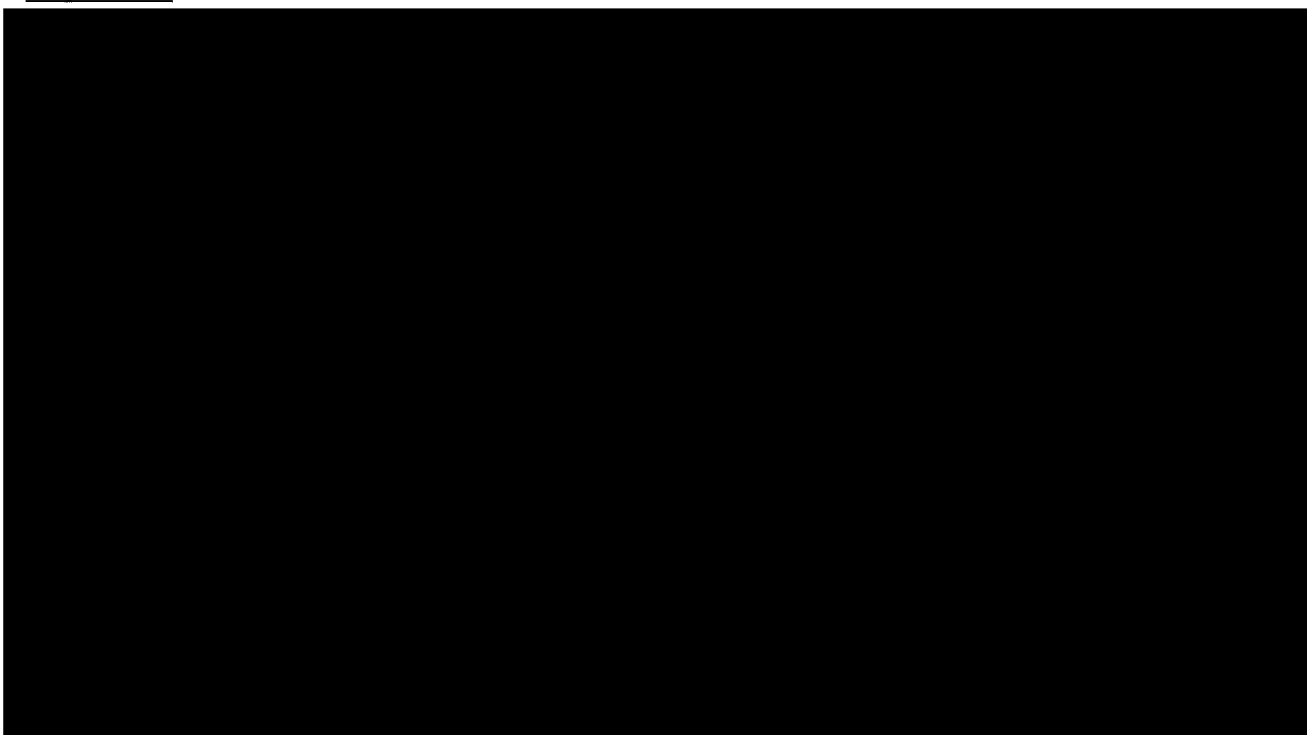
Myocarditis/Pericarditis in association with the Pfizer-BioNTech COVID-19 Vaccine- based on the following:

substantive number of cases that met the Bonaca criteria for definite, probable and possible myocarditis in the SMSR #5 most events are temporally related to the vaccination

Israel Ministry of Health¹ concluded a possible link between the second dose and the onset of myocarditis among young men (16-30), and that this link was highlighted to be stronger among the 16-19 younger age group.

that adolescents and the young adult population will soon be vaccinated in much larger numbers.

Response 1:



Comment 2

Discuss the timeline for alignment of the Reference Safety Information and the Canadian Product Monograph for the following events: Asthenia, Lethargy, Decreased appetite, Hyperhidrosis, Night sweats and Paresthesia. In addition, address any plans to include labelling updates from other jurisdictions, such as facial swelling in people with a history of injections with dermal fillers recommended by the European Medicines Agency.

Response 2:

Comment 3

In addition, please include the following in the next SMSR:

Provide an updated cumulative review of the following safety topics. Data should be stratified by sex, age, gender, dose 1 or dose 2 and assessed for causality using Brighton Collaboration Definition Criteria (or validated Definition Criteria). The observed and expected analyses should be included. An analysis of Canadian cases should be included. In addition, discuss the need for any potential amendment to the product monograph and/or the risk management plan and make, accordingly, a proposal for the changes to the relevant sections within this discussion.

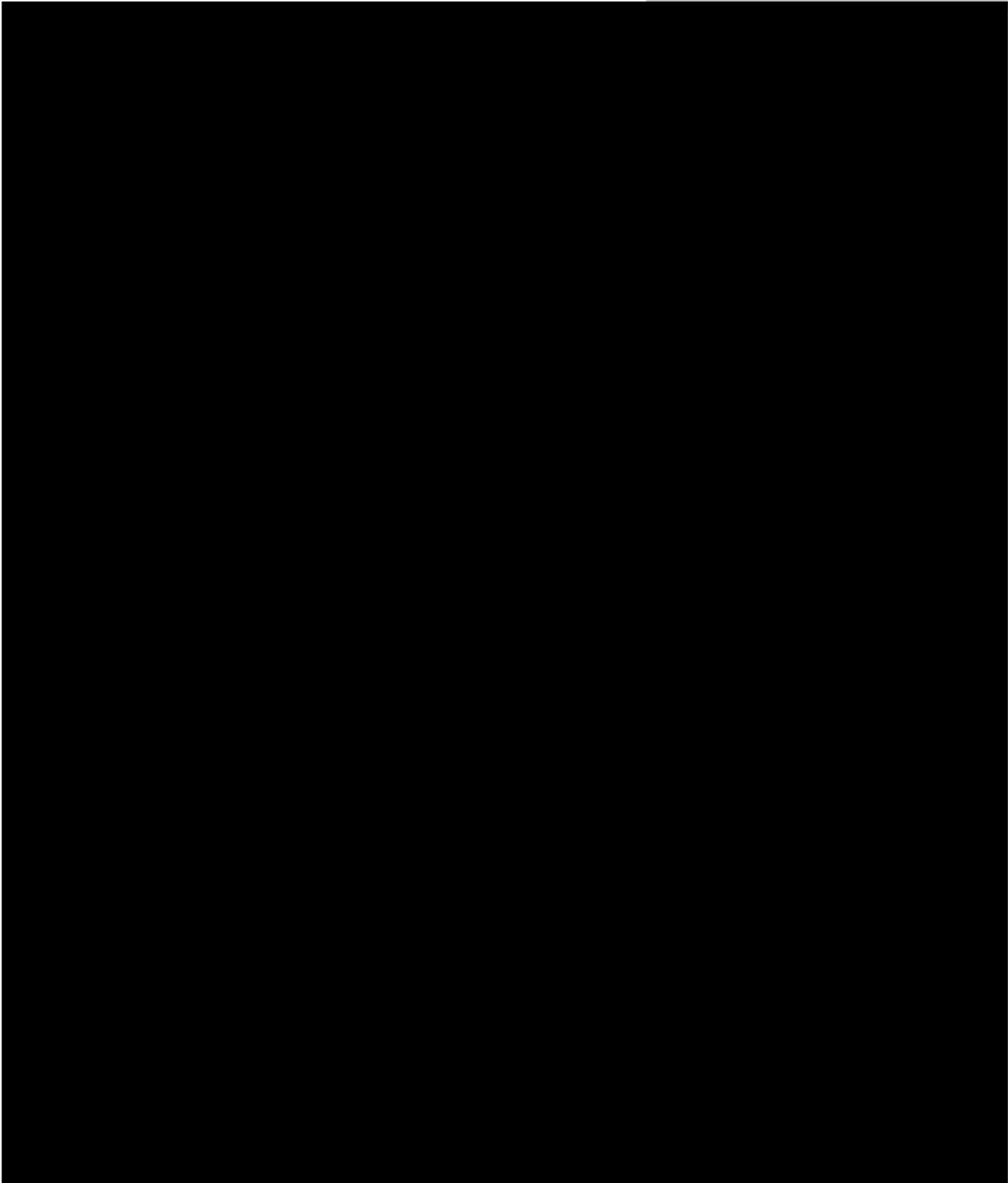
Cases of thrombosis with thrombocytopenia following vaccination with Pfizer BioNtech using appropriate SMQs to extract the cases including: thrombotic events with/without thrombocytopenia and thrombocytopenia without applying time limit specifications.

Cases of seizure following vaccination of Pfizer BioNtech vaccine. Search criteria should be included and encompass all generalized convulsive seizures following immunization.

Cases of hypertensive crisis with intracranial haemorrhage and provide a discussion regarding cases recently described in the literature.

Cases of hearing loss and trigeminal neuralgia, and provide a discussion regarding cases recently analyzed.

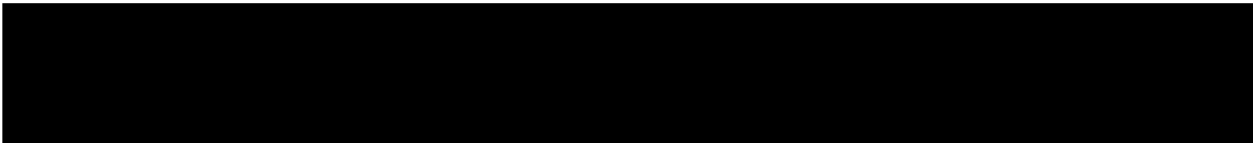
Response 3:



13 TERMS AND CONDITIONS

As stated in section 2, the Pfizer-BioNTech COVID-19 Vaccine is subject to terms and conditions that need to be met by the MAH. The compliance of the MAH to the terms and conditions relevant to adverse events reporting will be assessed below.

Terms and conditions	Met or not met
The monthly safety reports should be submitted within 15 days after the last day of a month, beginning after the first full calendar month after authorization.	
Interval and cumulative number of reports (serious and non-serious), overall and by age groups and in special populations (e.g. pregnant women)	
Interval and cumulative number of reports per HLT and SOC	
Number of reports in Canada and Global	
Exposure data, stratified by country, age groups, race and ethnicity	
Changes to reference safety information in the interval	
Ongoing and closed signals in the interval	
List of adverse events of special interest including the Safety Platform for Emergency Vaccines list and RMP safety concerns (including the additional missing information): reports – numbers and relevant cases, including time-to-onset and O/E analyses	
Fatal reports – numbers and relevant cases, including observed/expected analyses	
Vaccination failure / lack of efficacy (including confirmed and suspected cases) and errors – number relevant cases	
Potential interaction with other vaccines/concomitant treatments-number and relevant cases	
Summary outcomes of some of the routine pharmacovigilance activities (as presented in the EU RMP Part III and applied in the Canadian context) should be included for the purpose of rapid signal detection and communication activities. Summary of all ongoing studies can be included in the first six-month scheduled PBRER, unless a safety signal is identified that requires immediate regulatory action.	
Risk/benefit considerations	



14 COMPLIANCE ISSUES (GVP/GMP)

The section was not provided in this SMSR.

15 RECOMMENDATIONS

From Executive Summary

16 REFERENCES

The references are provided as footnotes and hyperlinks throughout the document.

17 APPENDICES

From: [REDACTED]
To: Alhaddad, Saj (HC/SC)
Cc: Hunt, Melissa (HC/SC); Rose, Jhona (HC/SC); eSubmissions-CA; [REDACTED]
Subject: RE: Pfizer-BioNTech COVID-19 Vaccine Monthly Summary Safety Report letter control# 251813
Date: 2021-06-07 8:37:37 PM
Attachments: Letter to MAH control number 251813, 252939.pdf

Dear Saj,

I confirm receipt of the attached request.

As we are currently working on finalizing and submitting our NDS this week, we will get back to you shortly regarding response timelines for the different requests.

Sincerely,

From: Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>

Sent: Monday, June 7, 2021 3:45 PM

To: eSubmissions-CA <eSubmissions-CA@pfizer.com>

Cc: Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>; Rose, Jhona (HC/SC) <jhona.rose@canada.ca>

Subject: [EXTERNAL] Pfizer-BioNTech COVID-19 Vaccine Monthly Summary Safety Report letter control# 251813

Dear [REDACTED]

As part of Health Canada's efforts to minimize health risk factors to Canadians while maximizing the safety provided by the regulatory system for health products, the Marketed Health Products Directorate (MHPD) has completed a comprehensive review of the Summary Monthly Safety Report (SMSR) covering the period from April 1, 2021 to April 29, 2021 for **the Pfizer-BioNTech COVID-19 Vaccine (tozinameran) control number 251813 and the Cumulative Analysis of Cardiac Failure and Myocardial Infarction Adverse Event Reports of (BNT162B2) through April 29, 2021 control number 252939**. Please find actions in the attached document stemming from this review and address them by the assigned timelines in the letter.

Please confirm receipt of this e-mail and the attached letter,

Thank you,

Saj Alhaddad

A/ Senior Regulatory Project Manager - Gestionnaire principal de projets réglementaires par intérim
Bureau of Biologics, Radiopharmaceuticals and Self-Care Products | Bureau des produits
biologiques, radiopharmaceutiques et de soins autoadministrés
Marketed Health Products Directorate - (MHPD) | Direction des produits de santé commercialisés -
(DPSC)

Saj.alhaddad@canada.ca

Tel : (613) 240-9514



Marketed Health Products Directorate
Address Locator # 1906A
OTTAWA, Ontario
K1A 0K9

Date: June 07, 2021

Control #: 251813, 252939

[REDACTED]
[REDACTED] Regulatory Affairs
Pfizer Canada ULC
17300 Trans-Canada Highway
KIRKLAND, Quebec
H9J 2M5

Email: ESUBMISSIONS-CA@PFIZER.COM

Dear [REDACTED]

Re: Pfizer-BioNTech COVID-19 Vaccine (tozinameran)

As part of Health Canada's efforts to minimize health risk factors to Canadians while maximizing the safety provided by the regulatory system for health products, the Marketed Health Products Directorate (MHPD) has completed a comprehensive review of the Summary Monthly Safety Report (SMSR) covering the period from April 1, 2021 to April 29, 2021 for **the Pfizer-BioNTech COVID-19 Vaccine (tozinameran) control number 251813 and the Cumulative Analysis of Cardiac Failure and Myocardial Infarction Adverse Event Reports of (BNT162B2) through April 29, 2021 control number 252939**. Please find below actions for Pfizer Canada ULC and BioNTech Manufacturing GmbH stemming from this review.

In accordance with the Risk Management Plan Terms and Conditions, imposed under the *Interim Order Respecting the Importation, Sale and Advertising of Drugs for Use in Relation to Covid-19*, Pfizer Canada ULC is required to submit monthly safety reports for the period of the Interim Order authorization. As such, you are requested to submit the monthly safety report for the period of **April 30, 2021 to May 31, 2021** including cumulative number of reports (serious and non-serious) and adverse events that occurred in Canada and globally for the **Pfizer-BioNTech COVID-19 Vaccine (tozinameran)** known to **Pfizer Canada ULC and BioNTech Manufacturing GmbH**.

Actions for Pfizer Canada ULC and BioNTech Manufacturing GmbH stemming from the SMSR #5 review are to:

To the MAH:

1. Discuss the need to submit a new Post-Authorization change – PM safety update and/or update the risk management plan regarding the following risks:



- a. **Facial paralysis /Bell's Palsy** in association with the Pfizer-BioNTech COVID-19 Vaccine, based on the imbalance observed in the clinical trials, increase in frequency of reporting from the post-market data, and safety information captured in the EMA-SmPC and EUA USPI (including Bell's Palsy).
- b. **Myocarditis/Pericarditis** in association with the Pfizer-BioNTech COVID-19 Vaccine- based on the following:
 - substantive number of cases that met the Bonaca criteria for definite, probable and possible myocarditis in the SMSR #5
 - most events are temporally related to the vaccination
 - Israel Ministry of Health¹ concluded a possible link between the second dose and the onset of myocarditis among young men (16-30), and that this link was highlighted to be stronger among the 16-19 younger age group.
 - that adolescents and the young adult population will soon be vaccinated in much larger numbers.
2. Discuss the timeline for alignment of the Reference Safety Information and the Canadian Product Monograph for the following events: *Asthenia, Lethargy, Decreased appetite, Hyperhidrosis, Night sweats* and *Paresthesia*. In addition, address any plans to include labelling updates from other jurisdictions, such as *facial swelling in people with a history of injections with dermal fillers* recommended by the European Medicines Agency.

In addition, please include the following in the next SMSR:

3. Provide an updated cumulative review of the following safety topics. Data should be stratified by sex, age, gender, dose 1 or dose 2 and assessed for causality using Brighton Collaboration Definition Criteria (or validated Definition Criteria). The observed and expected analyses should be included. An analysis of Canadian cases should be included. In addition, discuss the need for any potential amendment to the product monograph and/or the risk management plan and make, accordingly, a proposal for the changes to the relevant sections within this discussion.
 - a. **Cases of thrombosis with thrombocytopenia** following vaccination with Pfizer BioNtech using appropriate SMQs to extract the cases including: thrombotic events with/without thrombocytopenia and thrombocytopenia without applying time limit specifications.
 - b. **Cases of seizure** following vaccination of Pfizer BioNtech vaccine. Search criteria should be included and encompass all generalized convulsive seizures following immunization.
 - c. **Cases of hypertensive crisis with intracranial haemorrhage** and provide a discussion regarding cases recently described in the literature.
 - d. **Cases of hearing loss and trigeminal neuralgia**, and provide a discussion regarding cases recently analyzed.

¹ Surveillance of Myocarditis (Inflammation of the Heart Muscle) Cases Between December 2020 and May 2021 (Including) | Ministry of Health (www.gov.il)



A control number has been assigned for your submission of a monthly safety report in response to this letter. The control number is **253419**. Please provide the monthly safety report before or on **June 15, 2021** and include this control number in the cover letter of your response, along with a copy of this letter.

Sponsors must now submit their regulatory transactions using the Regulatory Enrolment Process (REP). By using this process, transactions in both eCTD and non-eCTD formats can be securely submitted via the Common Electronic Submissions Gateway (CESG).

Questions concerning this request should be directed to Saj Alhaddad, Acting Senior Regulatory Project Manager, BBRS, MHPD, by email at hc.mbbnhpb.rpmgpr.bpbbbsnc.sc@canada.ca.

Thank you in advance for your cooperation.

Melissa Hunt
Director
Marketed Health Products Directorate

This document has been signed electronically using the Health Canada docuBridge system. /
Ce document a été signé électroniquement à l'aide du système docuBridge de Santé Canada.

From: [Salem, Myriam \(HC/SC\)](#)
To: [Hunt, Melissa \(HC/SC\)](#); [Alhaddad, Saj \(HC/SC\)](#)
Cc: [Stothart, Tonja \(HC/SC\)](#)
Subject: RE: For Director Review/Signature Pfizer BioNtech vaccine MSR6 and letter to MAH (DSTS#253419)
Date: 2021-07-09 5:35:59 PM
Attachments: [253419 Pfizer BioNTech SMSR 6 MEMO to BRDD 0.1.docx](#)

Sorry for the multiple emails, I have corrected the Subject of the memo.

Thanks,
 Myriam

From: Salem, Myriam (HC/SC)
Sent: 2021-07-09 5:34 PM
To: Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>; Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>
Cc: Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>
Subject: RE: For Director Review/Signature Pfizer BioNtech vaccine MSR6 and letter to MAH (DSTS#253419)

Hi Melissa,
 Please find attached the corresponding memo for your review.
 Thanks,
 Myriam

From: Salem, Myriam (HC/SC)
Sent: 2021-07-09 4:32 PM
To: Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>; Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>
Cc: Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>
Subject: RE: For Director Review/Signature Pfizer BioNtech vaccine MSR6 and letter to MAH (DSTS#253419)

Thank you Melissa, I have updated the MSR, and addressed the comments. Will follow shortly with the memo for your review.
 Merci beaucoup,
 Myriam

From: Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>
Sent: 2021-07-09 3:30 PM
To: Salem, Myriam (HC/SC) <myriam.salem@canada.ca>; Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>
Cc: Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>
Subject: RE: For Director Review/Signature Pfizer BioNtech vaccine MSR6 and letter to MAH (DSTS#253419)

Hi Myriam,

I have a few additional changes and comments in the docubridge version. Also invite Tonja if anything additional.

I think we will likely wrap this up on Monday morning. As discussed we'll need a memo to BRDD for the labelling changes too.

Thank you so very much!

Melissa

From: Salem, Myriam (HC/SC) <myriam.salem@canada.ca>
Sent: 2021-07-09 10:52 AM
To: Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>; Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>
Cc: Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>
Subject: RE: For Director Review/Signature Pfizer BioNtech vaccine MSR6 and letter to MAH (DSTS#253419)

Thank you Saj,

Please find below the corrected link:

[HC6-024-e243022 \(1.0\) Reg Info - Post Market Tracker](#)

Thanks,

Myriam

From: Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>
Sent: 2021-07-09 10:38 AM
To: Salem, Myriam (HC/SC) <myriam.salem@canada.ca>; Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>
Cc: Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>
Subject: RE: For Director Review/Signature Pfizer BioNtech vaccine MSR6 and letter to MAH (DSTS#253419)

Thank you for giving me access Myriam,

Both of these documents are identical, I think you accidentally dragged and dropped the same thing. FYI the report is from April 30 to May 31 if we wish to make that edit on the cover page of the report.

I will add the control number as soon as you re-upload the letter to MAH.

Regards,

Saj

From: Salem, Myriam (HC/SC) <myriam.salem@canada.ca>
Sent: 2021-07-09 10:28 AM
To: Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>
Cc: Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>; Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>
Subject: For Director Review/Signature Pfizer BioNtech vaccine MSR6 and letter to MAH (DSTS#253419)

Hi Melissa,

Please note that the Summary Monthly Safety Report #6 and letter to MAH for Pfizer-BioNtech were uploaded to docuBridge for your review and signature.

[HC6-024-e243022 \(1.0\) Reg Info - Post Market Tracker](#)

[HC6-024-e243022 \(1.0\) Reg Info - Post Market Tracker](#)

The documents were also shared with Saj and Tonja.

Thank you,

Myriam



Health Santé
Canada Canada

**Health Products and Food Branch
Direction générale des produits de santé et des aliments**

Marketed Health Products Directorate	The Marketed Health Products Directorate (MHPD) is responsible for coordination of consistency of post-market surveillance and assessment of signals and safety trends concerning all marketed health products.
Direction des produits de santé commercialisés	La Direction des produits de santé commercialisés (DPSC) est chargée de la coordination et la cohérence des activités de surveillance post-approbation et d'évaluer les signaux et les tendances concernant l'innocuité de tous les produits de santé commercialisés.

MEMORANDUM

NOTE DE SERVICE

TO : Leo Bouthillier, PhD
À Director
Centre for Evaluation of
Radiopharmaceuticals and
Biotherapeutics (CERB)
Biologic and Radiopharmaceutical
Drugs Directorate (BRDD)

FROM : Melissa Hunt
DE Director
Marketed Health Products
Directorate (MHPD)

SECURITY - CLASSIFICATION - DE SÉCURITÉ

OUR FILE - NOTRE RÉFÉRENCE

YOUR FILE - VOTRE RÉFÉRENCE

DATE

July 09, 2021

SUBJECT : Review of Myocarditis and the PFIZER-BIONTEH COVID-19 Vaccine
OBJET and COVID-19 MODERNA Vaccine

- ☐ No Action Required—FYI Only
- ☒ Recommended For Immediate Action
- ☐ Recommended For Action Post Approval/at Next Opportunity

Memorandum

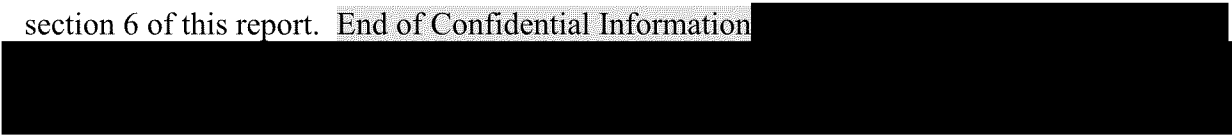
-2-

The Bureau of Biologics, Radiopharmaceuticals and Self-Care Products (BBRS) of the Marketed Health Products Directorate (MHPD) reviewed the 5th and 6th Summary Monthly Safety Reports for the Pfizer-BioNTech COVID-19 Vaccine covering the months of April (April 01, 2021 to April 29, 2021) and May 2021 (April 30, 2021 to May 31, 2021) respectively. During these reporting periods the MAH discussed several safety topics, 16 Adverse Events of Special Interest (AESI).

Following the review of the data provided in the MSR#5¹ the MHPD did not agree with the MAH's assessment leading to closure of the signals on facial paralysis. Therefore, the MHPD requested in a letter sent to the MAH on June 07, 2021 a discussion regarding the need to submit a new *Post-Authorization change – PM safety update and/or update the risk management plan* regarding the risk of Facial paralysis /Bell's Palsy based on the imbalance observed in the clinical trials follow-up, increase in frequency of reporting from the post-market data, and safety information captured in other jurisdictions. Facial Paralysis and/or Bell's Palsy is labeled in the Clinical adverse reaction section of the EMA-SmPC and EUA USPI (including Bell's Palsy). The MHRA Pfizer Summary of Product Characteristics also includes acute peripheral facial paralysis as an ADR with a frequency of 1:1000.

The possible labelling of these events was discussed in a meeting with Pfizer Canada and BRDD on June 21, 2021.

Three additional serious cases of Bell's Palsy were reported in the MSR#6² submitted on June 15, 2021. Bell's Palsy is an AESI that is closely monitored in Canada by the PHAC and MHPD. Up to June 25, 2021, 145 cases of Bell's palsy were reported to the Canadian databases, including cases meeting the Brighton Collaboration criteria for diagnosis level 1 to 4. **Beginning of Confidential Information** Cases of Bell's Palsy following immunization with Pfizer BioNTech vaccine were statistically disproportionally reported in the Canadian databases as discussed in section 6 of this report. **End of Confidential Information**

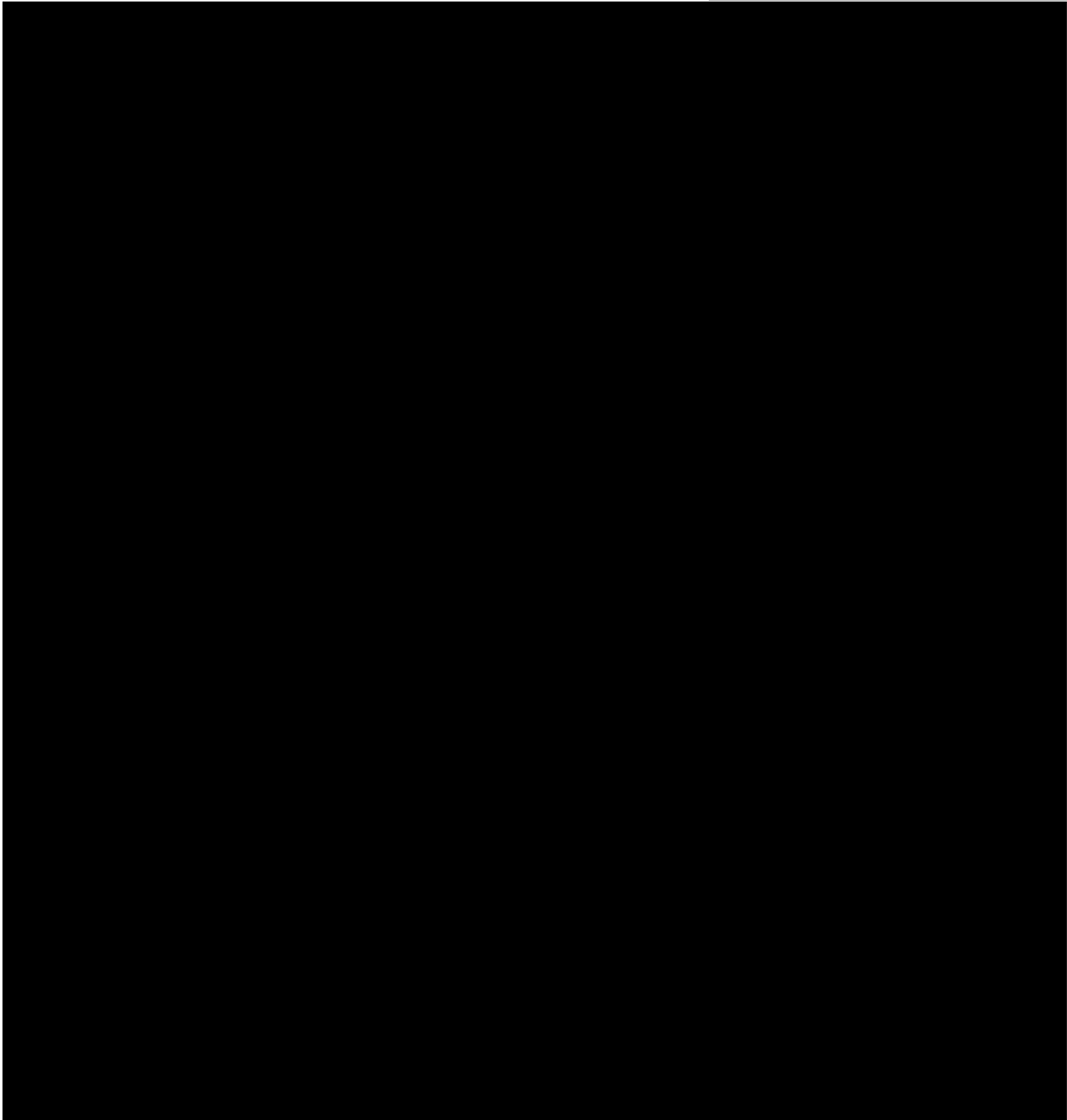


Overall, the MAH should be requested to submit a new Post-Authorization change – PM safety update the risk of facial paralysis/Bell's Palsy, based on the previous assessment showing an imbalance in Clinical trials, labelling in other jurisdictions and given that serious Canadian cases have been reported following immunization with the Pfizer BioNTech vaccine including cases corresponding to the Brighton Collaboration level 1 to 4.

¹ DSTS#251813, HC6-024-e243022 (1.0) Reg Info - Post Market Tracker

² DSTS#253419,) HC6-024-e243022 (253419 - Response to MHPD request dated 2021-06-07 (April 30 to May 31, 2021)) - Summary Monthly Safety Report 6 30-APR-2021 through 31-May-2021

Memorandum



This document has been signed electronically using the Health Canada docuBridge system. /
Ce document a été signé électroniquement à l'aide du système docuBridge de Santé Canada.

From: [Salem, Myriam \(HC/SC\)](#)
To: [Hunt, Melissa \(HC/SC\)](#); [Alhaddad, Saj \(HC/SC\)](#)
Cc: [Stothart, Tonja \(HC/SC\)](#); [Rose, Jhona \(HC/SC\)](#)
Subject: RE: For Director Review/Signature Pfizer BioNtech vaccine MSR6 and letter to MAH (DSTS#253419)
Date: 2021-07-12 9:44:26 AM
Attachments: [253419 Pfizer BioNTech SMSR 6 MEMO to BRDD 0.2.docx](#)

Hi Melissa,

Thank you, I have updated/cleaned the MSR and letter on docuBridge and attached the memo for your review. I will upload the memo as soon as it is approved.

Thanks,
 Myriam

From: Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>
Sent: 2021-07-12 6:48 AM
To: Salem, Myriam (HC/SC) <myriam.salem@canada.ca>; Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>
Cc: Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>; Rose, Jhona (HC/SC) <jhona.rose@canada.ca>
Subject: RE: For Director Review/Signature Pfizer BioNtech vaccine MSR6 and letter to MAH (DSTS#253419)

Hi Myriam,

I made minor comments in the Exec Summary and I tried to match the letter to the exec summary. Can you take a look? We're almost ready to go 😊

Then if these could be reflected in the BRDD memo that would be great.

Jhona- This is done and you don't need to do anything. 😊 Just FYI that in discussions with BRDD last week we decided that for any labelling updated we would consistently send a memo to BRDD to action (and then raise at our bilats to make sure on the radar). We did not do that for AZ last week (we put general recommendation in our letter following MSSR), but we checked with BRDD before that.

Thanks!
 Melissa

From: Salem, Myriam (HC/SC) <myriam.salem@canada.ca>
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Subject: For Director Review/Signature Pfizer BioNtech vaccine MSR6 and letter to MAH (DSTS#253419)

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Thank you,

Myriam



Health Santé
Canada Canada

**Health Products and Food Branch
Direction générale des produits de santé et des aliments**

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MEMORANDUM

NOTE DE SERVICE

TO : Leo Bouthillier, PhD
À Director
Centre for Evaluation of
Radiopharmaceuticals and
Biotherapeutics (CERB)
Biologic and Radiopharmaceutical
Drugs Directorate (BRDD)

FROM : Melissa Hunt
DE Director
Marketed Health Products
Directorate (MHPD)

SECURITY - CLASSIFICATION - DE SÉCURITÉ

OUR FILE - NOTRE RÉFÉRENCE

YOUR FILE - VOTRE RÉFÉRENCE

DATE

July 12, 2021

SUBJECT : Review of MSR#5 and MSR#6 on facial paralysis for the PFIZER-
OBJET BIONTEH COVID-19 Vaccine and COVID-19 MODERNA Vaccine

- ☐ No Action Required—FYI Only
- ☒ Recommended For Immediate Action
- ☐ Recommended For Action Post Approval/at Next Opportunity

Memorandum

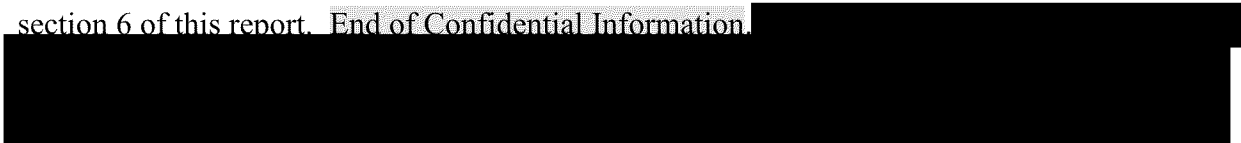
-2-

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Three additional serious cases of Bell's Palsy were reported in the MSR#6² submitted on June 15, 2021. Bell's Palsy is an AESI that is closely monitored in Canada by the PHAC and MHPD. Up to June 25, 2021, 145 cases of Bell's palsy were reported to the Canadian databases, including cases meeting the Brighton Collaboration criteria for diagnosis level 1 to 4. **Beginning of Confidential Information** Cases of Bell's Palsy following immunization with Pfizer BioNTech vaccine were statistically disproportionally reported in the Canadian databases as discussed in section 6 of this report. **End of Confidential Information.**



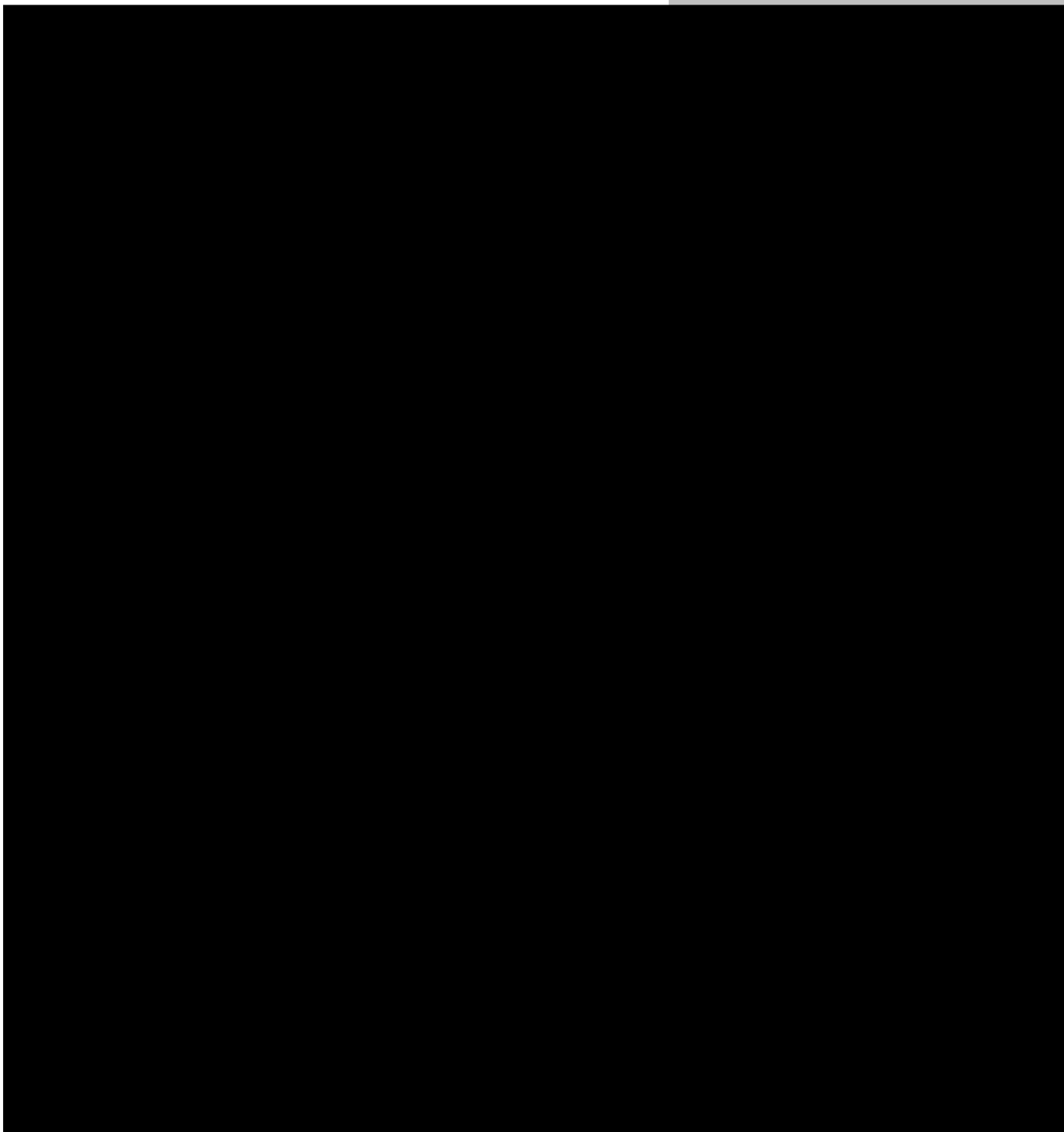
Overall, the MAH should be requested to submit a new Post-Authorization change – PM safety update the risk of facial paralysis/Bell's Palsy, based on the previous assessment showing an imbalance in Clinical trials, labelling in other jurisdictions and given that serious Canadian cases have been reported following immunization with the Pfizer BioNTech vaccine including cases corresponding to the Brighton Collaboration level 1 to 4.

¹ DSTS#251813, HC6-024-e243022 (1.0) Reg Info - Post Market Tracker

² DSTS#253419,) HC6-024-e243022 (253419 - Response to MHPD request dated 2021-06-07 (April 30 to May 31, 2021)) - Summary Monthly Safety Report 6 30-APR-2021 through 31-May-2021

Memorandum

-2-



³ <https://www.gov.uk/government/publications/regulatory-approval-of-pfizer-biontech-vaccine-for-covid-19/information-for-healthcare-professionals-on-pfizerbiontech-covid-19-vaccine>

⁴ <https://www.fda.gov/media/144413/download>

⁵ https://www.ema.europa.eu/en/documents/product-information/comirnaty-epar-product-information_en.pdf

Memorandum

-2-

Document Released Under the Access to Information

This document has been signed electronically using the Health Canada docuBridge system. /
Ce document a été signé électroniquement à l'aide du système docuBridge de Santé Canada.

From: [REDACTED]
To: Alhaddad, Saj (HC/SC)
Cc: Hunt, Melissa (HC/SC); Rose, Jhona (HC/SC); [REDACTED]
Subject: RECEIPT CONFIRMATION: Pfizer-BioNTech COVID-19 Vaccine Monthly Summary Safety Report letter control# 253419
Date: 2021-07-13 9:35:42 AM
Attachments: [253419 Letter to MAH.pdf](#)

Dear Saj
We confirm receipt of the below request.
Sincerely,
[REDACTED]

From: Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>
Sent: Monday, July 12, 2021 9:02 PM
To: eSubmissions-CA <eSubmissions-CA@pfizer.com>
Cc: Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>; Rose, Jhona (HC/SC) <jhona.rose@canada.ca>
Subject: [EXTERNAL] Pfizer-BioNTech COVID-19 Vaccine Monthly Summary Safety Report letter control# 253419

Dear [REDACTED]
As part of Health Canada's efforts to minimize health risk factors to Canadians while maximizing the safety provided by the regulatory system for health products, the Marketed Health Products Directorate (MHPD) has completed a comprehensive review of the Summary Monthly Safety Report (SMSR) covering the period from April 30, 2021 to May 31, 2021 for **the Pfizer-BioNTech COVID-19 Vaccine (tozinameran) control number 253419**. Please find below actions for Pfizer Canada ULC and BioNTech Manufacturing GmbH stemming from this review.
Please use the assigned control number for your next Monthly Safety report, and submit the attached letter in module 1.0.3 in your sequence.
Please confirm receipt of this e-mail and the attached letter,
Thank you,

Saj Alhaddad

A/ Senior Regulatory Project Manager - Gestionnaire principal de projets réglementaires par intérim
Bureau of Biologics, Radiopharmaceuticals and Self-Care Products | Bureau des produits biologiques, radiopharmaceutiques et de soins autoadministrés
Marketed Health Products Directorate - (MHPD) | Direction des produits de santé commercialisés - (DPSC)
Saj.alhaddad@canada.ca
Tel : (613) 240-9514



Marketed Health Products Directorate
Address Locator # 1906A
OTTAWA, Ontario
K1A 0K9

Date: July 12, 2021

Control #: 253419

[REDACTED]
Regulatory Affairs
Pfizer Canada ULC
17300 Trans-Canada Highway
KIRKLAND, Quebec
H9J 2M5

Email: ESUBMISSIONS-CA@PFIZER.COM

Dear [REDACTED]

Re: Pfizer-BioNTech COVID-19 Vaccine (tozinameran)

As part of Health Canada's efforts to minimize health risk factors to Canadians while maximizing the safety provided by the regulatory system for health products, the Marketed Health Products Directorate (MHPD) has completed a comprehensive review of the Summary Monthly Safety Report (SMSR) covering the period from April 30, 2021 to May 31, 2021 for **the Pfizer-BioNTech COVID-19 Vaccine (tozinameran) control number 253419**. Please find below actions for Pfizer Canada ULC and BioNTech Manufacturing GmbH stemming from this review.

In accordance with the Risk Management Plan Terms and Conditions, imposed under the *Interim Order Respecting the Importation, Sale and Advertising of Drugs for Use in Relation to Covid-19*, Pfizer Canada ULC is required to submit monthly safety reports for the period of the Interim Order authorization. As such, you are requested to submit the monthly safety report for the period of **June 01, 2021 to June 30, 2021** including cumulative number of reports (serious and non-serious) and adverse events that occurred in Canada and globally for the **Pfizer-BioNTech COVID-19 Vaccine (tozinameran)** known to **Pfizer Canada ULC and BioNTech Manufacturing GmbH**.

Actions for Pfizer Canada ULC and BioNTech Manufacturing GmbH stemming from the SMSR #6 review are to:

1. **Facial paralysis /Bell's Palsy:** From Pfizer's response to the letter issued on June 7, 2021, the following were noted: *With regards to the question on Facial paralysis /Bell's Palsy in association with the Pfizer-BioNTech COVID-19 Vaccine, the analysis on overall data in subjects reporting facial paralysis/Bell's palsy after BNT162b2 vaccination, including clinical study data, postauthorization reports and observed to expected analyses, provides inconclusive evidence of a causal association with BNT162b2. Evaluations will continue and*



Bell's palsy is an endpoint in Pfizer's observational surveillance studies. Updates to labeling language will be proposed if warranted upon future assessment.

Health Canada would like to reiterate that based on the imbalance observed in the clinical trials, increase in frequency of reporting from the post-market data, and safety information captured in the EMA SmPC, EUA USPI (including Bell's Palsy) and MHRA, Health Canada's position remains the same and the need for further risk mitigation will be discussed with our pre-market colleagues.

2. In addition, the Pfizer's response to the letter issued on June 7, 2021 noted the following: *All planned safety-related updates to the Core Data Sheet are captured in the Summary Monthly Safety Report (SMSR). As mentioned at the pre-New Drug Submission (NDS) meeting held with Health Canada (HC) on 3 June 2021, Pfizer plans on requesting a meeting with HC in the coming weeks to discuss upcoming revisions to the Product Monograph which will be filed under the second roll of the NDS CV as well as in parallel via an Interim Order Amendment.*

It is our understanding from the conversation on June 21, 2021 that Pfizer will soon submit a post-market label update to align labelling with the Core Data Sheet.

3. Include in the SMSR to be submitted by August 15, 2021:
 - a. A cumulative review of the following safety topics given the seriousness of the cases including fatalities
 - b. Cardiovascular events namely, myocardial infarction, cardiac failure
 - c. Seizure (using the search criteria identified previously by HC)
 - d. Arterial Thromboembolic events (Stroke)
 - e. Venous Thromboembolic events (deep venous thrombosis [DVT] and pulmonary embolism [PE]), using: the Standard MedDRA Query (SMQ) narrow "Embolic and thrombotic events, venous"

Data should be stratified by sex, age, gender, dose 1 or dose 2 and assessed for causality using Brighton Collaboration Definition Criteria. The observed and expected analyses should be included. An analysis of Canadian cases including an assessment on causality is also requested. Once the assessment is completed the MAH should also provide a discussion on the need to update the product monograph and/or update the risk management plan.

4. Discuss the need to implement a registry with reference in the CPM for pregnant women given that cases with serious outcomes are being reported to the Canadian databases. This approach will be consistent with the other COVID vaccines currently available in Canada. .



As a general reminder, a Notification of Foreign Action should be submitted to the MHPD in accordance with subsection C.01.050 of the *Food and Drug Regulations*, when appropriate. When safety updates are implemented in other jurisdictions Health Canada would like consideration to be given by the MAH with regards to implementation of these updates in the Canadian Product Monograph. In Addition, please provide the safety reports prepared for other regulatory agencies with the MSSR submissions.

A control number has been assigned for your submission of a monthly safety report in response to this letter. The control number is **254572**. Please provide the monthly safety report before or on **July15, 2021** and include this control number in the cover letter of your response, along with a copy of this letter.

Sponsors must now submit their regulatory transactions using the Regulatory Enrolment Process (REP). By using this process, transactions in both eCTD and non-eCTD formats can be securely submitted via the Common Electronic Submissions Gateway (CESG).

Questions concerning this request should be directed to Saj Alhaddad, Acting Senior Regulatory Project Manager, BBRS, MHPD, by email at hc.mbbnhpb.rpmgpr.bpbbnsnc.sc@canada.ca.

Thank you in advance for your cooperation.

Melissa Hunt
Director
Marketed Health Products Directorate

This document has been signed electronically using the Health Canada docuBridge system. /
Ce document a été signé électroniquement à l'aide du système docuBridge de Santé Canada.

From: Alhaddad, Saj (HC/SC)
To: HPFB-COVID19-DGPSSA (HC/SC)
Cc: Hunt, Melissa (HC/SC); Rose, Jhona (HC/SC)
Subject: RE: REMINDER: COVID-19 Drugs and Devices Report
Date: 2021-07-14 9:13:08 AM
Attachments: COVID-19 Drugs and Devices Chapter 4_2021-07-07.docx

MHPD's COVID-19 vaccine's team updates annotated and attached. Saj

From: HPFB-COVID19-DGPSSA (HC/SC) <hc.hpfb-covid19-dgpsa.sc@canada.ca>

Sent: 2021-07-14 8:58 AM

To: HPFB-COVID19-DGPSSA (HC/SC) <hc.hpfb-covid19-dgpsa.sc@canada.ca>; Basta, Patricia (HC/SC) <patricia.basta@canada.ca>; Curtis, Kaitlin (HC/SC) <kaitlin.curtis@canada.ca>; Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>; Akel, Sereen H (HC/SC) <sereenh.akel@canada.ca>; Antonio, Christopher (HC/SC) <christopher.antonio@canada.ca>; Panetta, Vincent (HC/SC) <vincent.panetta@canada.ca>; Tang, Marianne (HC/SC) <marianne.tang@canada.ca>; Sun, Rong (HC/SC) <rong.sun@canada.ca>; Proulx, Mathieu (HC/SC) <mathieu.proulx@canada.ca>; Dion, Catherine (HC/SC) <catherine.dion@canada.ca>; Punch, Vincent (HC/SC) <vincent.punch@canada.ca>; HC.F ORA_COVID / BAR_COVID F.SC <hc.ora_covid-bar_covid.sc@canada.ca>; HC.F MDD Issues / DIM Enjeux F.SC <hc.mddissues-dimenjeux.sc@canada.ca>; HC.F MHPD Action Requests F.SC <MHPD_Action_Requests@canada.ca>; Keene, Daniel (HC/SC) <daniel.keene@canada.ca>; Dillon, Kyle (HC/SC) <kyle.dillon@canada.ca>; McLean, Martin (HC/SC) <martin.mclean@canada.ca>; Wright-Gilbert, Sarah (HC/SC) <sarah.wright-gilbert@canada.ca>; McGrath, Eva (HC/SC) <eva.mcgrath@canada.ca>; Dillon, Kyle (HC/SC) <kyle.dillon@canada.ca>; Lefebvre, Larissa (HC/SC) <larissa.lefebvre@canada.ca>

Subject: RE: REMINDER: COVID-19 Drugs and Devices Report

Good morning,

This is a friendly reminder to please provide your weekly input **by CoB today**.

Last week's report is attached for your reference.

Thank you

Brennan Graham

COVID-19 Regulatory Response Team | Équipe d'intervention réglementaire de la COVID-19
 Health Products and Food Branch | Direction générale des produits de santé et des aliments
 613-406-4725

COVID-19: Drugs and Devices

Chapter 4: July 7, 2021

PREVIOUS REPORTS:

Refer to COVID-19: Drugs and Devices Chapter 1 for reporting from February 28th through May 29th 2020.

Refer to COVID-19: Drugs and Devices Chapter 2 for reporting from June 1st 2020 to August 27th 2020

Refer to COVID-19: Drugs and Devices Chapter 3 for reporting from September 4, 2020 to December 22, 2020

(This document is updated weekly on Thursdays)¹

This document summarizes the drugs and devices currently in development or authorized for COVID-19 and Health Canada's related regulatory activities. Several existing drugs or drug combinations are being repurposed and are being tested in human clinical trials in Canada and internationally. Numerous devices are now available through an Interim Order that allows expedited access to COVID-19 related medical devices. To date, Health Canada has authorized five vaccines (Pfizer-BioNTech, Moderna, AstraZeneca, COVISHIELD & Janssen) and two treatments (Remdesivir & Bamlanivimab) for use against COVID-19

¹ The information compiled in this document is from applications filed with Health Canada and other reputable sources, such as ClinicalTrials.gov, the World Health Organization's Clinical Trials Registry Platform, literature journals, or regulatory websites, and not from the media.

KEY UPDATES FROM LAST WEEK'S REPORT

DRUGS & NHPs		
Authorizations	Total	change
Clinical Trials	104	0
• Under IO	30	0
Disinfectants	312	0
• w/ direct claims against COVID-19	103	0
• Applications in queue	63	0
Hand Sanitizer (total)	4555	0
• Natural Health Product (NHP)	4423	0
• Over the Counter (OTC)	132	0
Site licenses for OTC drugs and NHP	2042	0

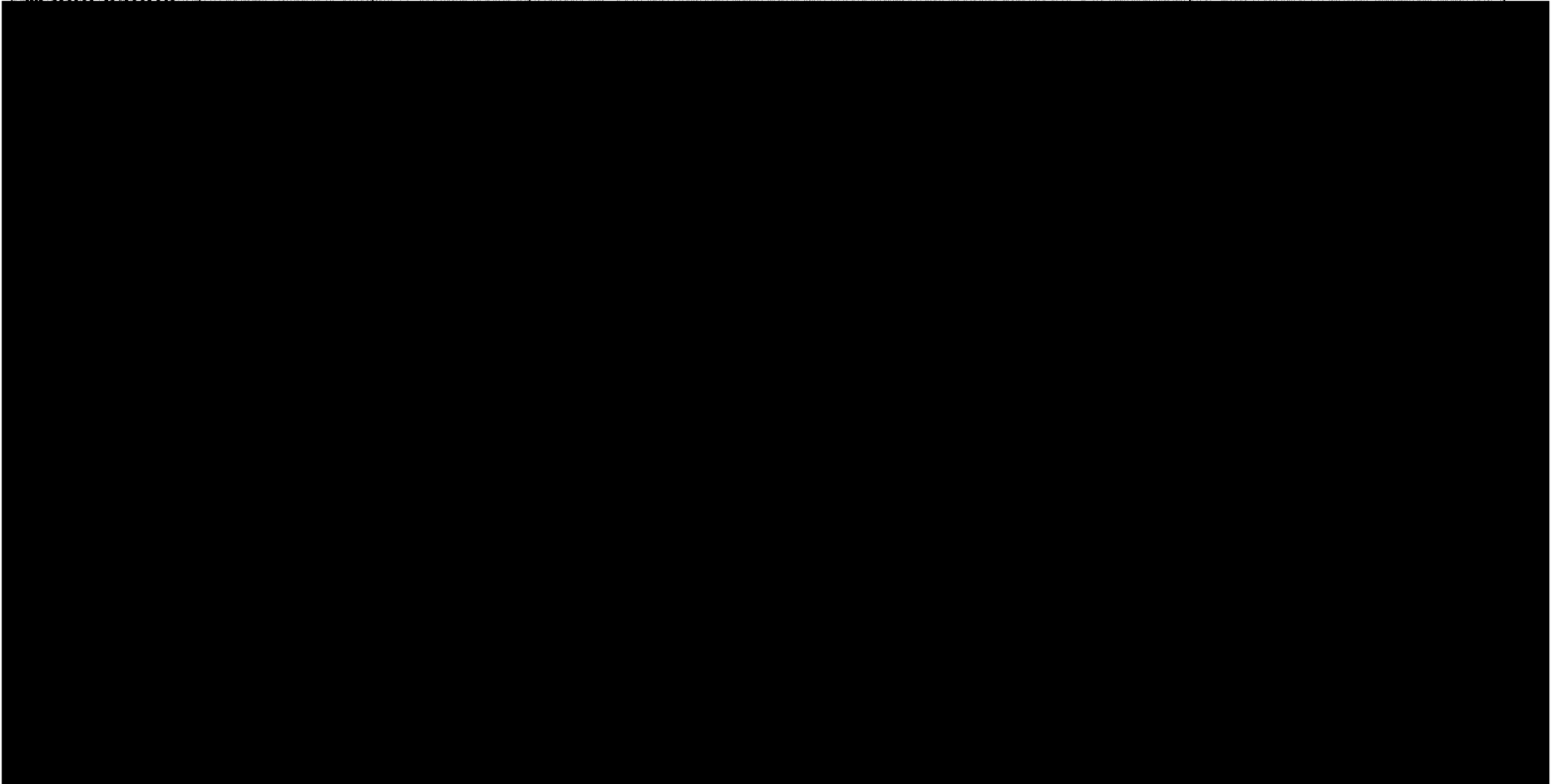
MEDICAL DEVICES		
Authorizations	Total	change
Devices (all)	706	+1
Test kits	76	+1
Non-in vitro diagnostic devices (total)	630	
• Respirators	69	0
• PPE - masks	88	0
• Face shields	140	0
• Ventilators	21	0
• Gloves	37	0
• Decontamination device	12	0
• Syringes	39	0
• Other ¹	224	0
Investigational Testing Applications (ITAs)	29	0
• Under IO	15	0
• Under MDR	14	0
Applications	Total	change
Test Kits		
• Under review and in screening	116	-2
• Incomplete applications	32	+4
Non-in vitro diagnostic devices	157	-7
ITAs being processed	10	+1

RECENT ACTIONS AND COMMUNICATIONS

- On July 2nd, MDD authorized the Solana SARS-CoV-2 Assay a lab-based device. Manufactured by Diagnostic Hybrids, Inc. - Also Trading As Quidel Corporation (United States).
- Note: this report does not include updates from NNHPD this week.

Vaccines and Treatments

AUTHORIZED UNDER THE INTERIM ORDER FOR SALE, IMPORTATION AND ADVERTISING OF DRUGS (ISAD)				
Sponsor/ Manufacturer	Product	Type	Status	Updates



ATIA - 20(1)(b)

ATIA - 20(1)(c)

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Pfizer Canada ULC/BioNtech	Tozinameran or BNT162b2	Vaccine (mRNA)	First vaccine approved under drugs IO Authorized December 9, 2020, with terms and conditions, for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome	

ATIA - 20(1)(b)

ATIA - 20(1)(c)

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			<p>coronavirus 2 (SARS- CoV-2) in individuals 16 years of age and older.</p> <p>On May 5, Health Canada authorized an amendment to expand the indication to adolescent population aged 12-15.</p>	
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ATIA - 20(1)(b)

ATIA - 20(1)(c)

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ATIA - 20(1)(b)

ATIA - 20(1)(c)

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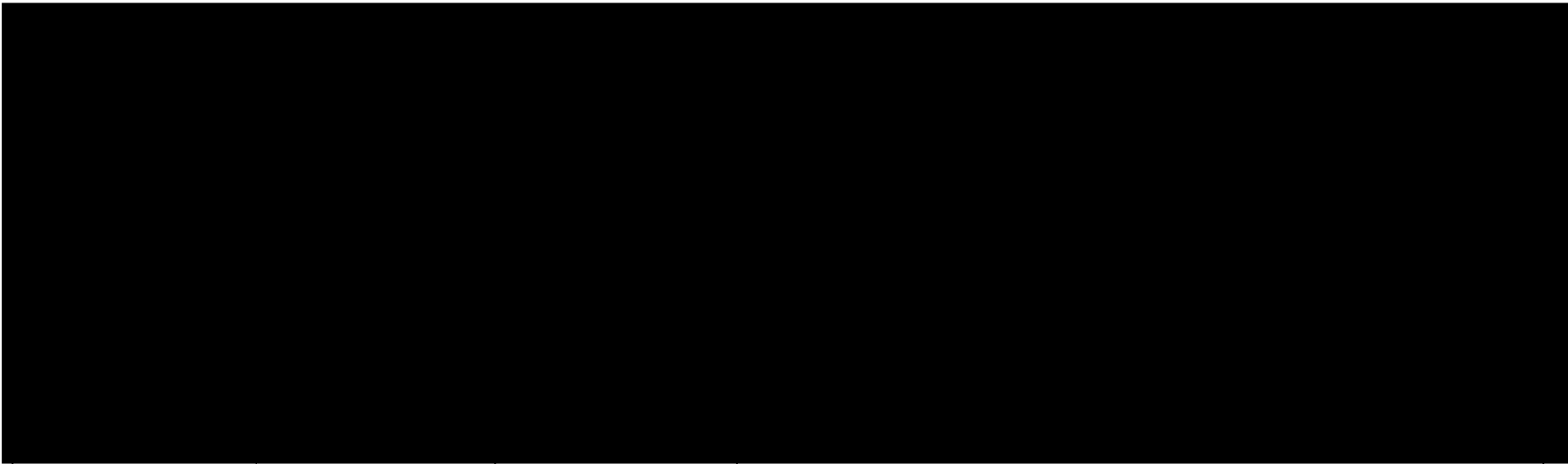
ATIA - 20(1)(b)

ATIA - 20(1)(c)

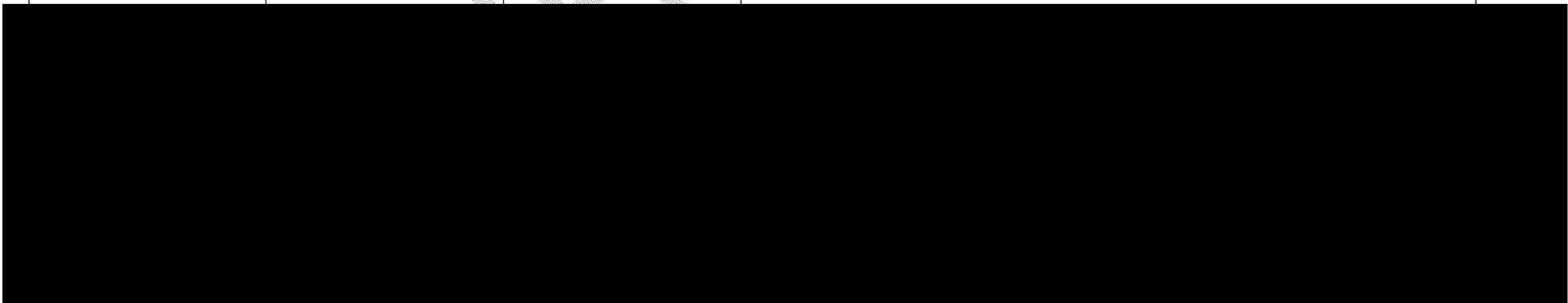
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UNDER REVIEW – Food & Drug Regulations (transition from the Interim Order)			
Sponsor/ Manufacturer	Product	Type	Status
Pfizer Canada ULC/BioNtech	Tozinameran or BNT162b2	Vaccine (mRNA)	Rolling Submission (filed under F&DR) Received June 10, 2021



Safety and Post-Market Surveillance

Adverse Events

From January 1 to June 23, 2021, a total of 37,662 Canadian (domestic) post-market adverse reaction (AR) reports have been received by the Canada Vigilance Program (CVP) and entered into the Canada Vigilance database (79,649 reports for 2020).

Section 1: Off-Label Use - Adverse reaction reports of drugs used to treat COVID-19 – Retrieved by reported indication of suspect drug(s) as of March 31, 2021:

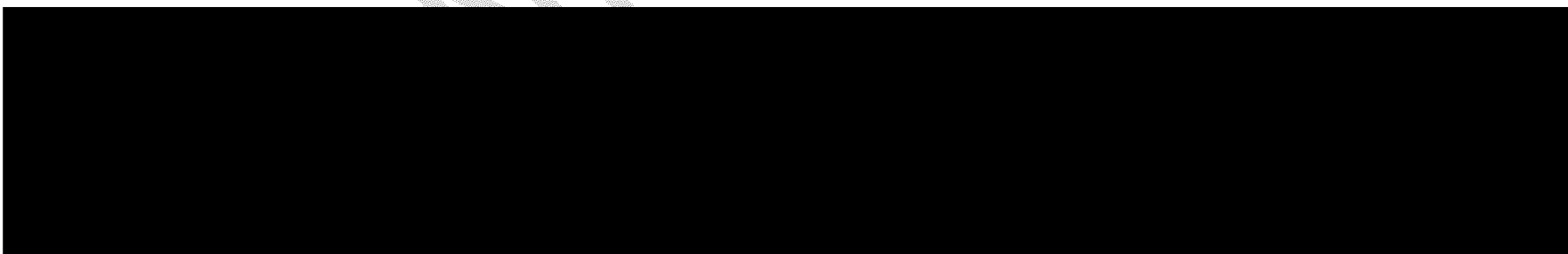
- One new domestic AR report was received in the past 7 days. Cumulative total of 26 reports received by the CVP as of June 30, 2021.
- All post-market AR reports are searched for any drugs that have a reported indication of coronavirus infection.

Section 2: Approved Treatments For COVID-19



Section 3: Approved Vaccines for COVID-19:

- **Pfizer-BioNtech COVID-19 Vaccine** (tozinameran) – Approved via interim order 2020-12-09: 121 new domestic AEFI reports received in the past 7 days. Cumulative total of 1,242 domestic reports received by the CVP as of June 30, 2021.



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N.B. Adverse Events Following Immunization (AEFI) are submitted to the Canadian Adverse Event Following Immunization Surveillance System (CAEFISS) at the Public Health Agency of Canada and reports from Market Authorization Holders are submitted to Health Canada's Canada Vigilance (CV) database. Occasionally consumers or health care providers may submit AEFI reports to Health Canada which are then maintained in the Canada Vigilance Database.

Drug Safety Surveillance

Safety issues (& drugs) covered in the COVID-19 articles screened bi-weekly:

- COVID-19 outcomes, including hospitalization and/or mortality (azithromycin, renin-angiotensin-aldosterone system inhibitors, ascorbic acid, corticosteroids, quetiapine, haloperidol, beta blockers, calcium channel blockers)
- Pulmonary embolism (warfarin, azithromycin)
- Risk of SARS-CoV-2 infection (calcium channel blockers)
- Decreased immune response to SARS-CoV-2 vaccine (mycophenolate mofetil)

Monitoring of Advertising Related to COVID-19

False and Misleading Claims related to COVID-19:

- As of July 2, the results of Health Canada's proactive monitoring of online sources for false and misleading claims related to the prevention, diagnosis or treatment of COVID-19 are as follows:
 - 25,571 [+32 compared to last week] cases of potential non-compliance have been identified. These involve the following product types: medical devices (1009) [+1], NHPs (408) [no change], OTCs (345) [+1], prescription (13) [no change]
 - 736 [+2] regulatory letters are in preparation or have been issued for authorized products making unauthorized claims
 - 368 [no change] referrals have been made to ROEB for unauthorized products
 - No action was required in 24,262 [+30] cases

Stakeholder Communications and Web Publications

- Auto published daily updates to List of authorized medical devices other than testing devices, List of applications under evaluation and List of authorized testing devices

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Document Released Under the Access to Information

- Published weekly updates to the list of authorized hand sanitizers

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KEY RESOURCES

Updated as needed:

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- COVID-19 vaccines and treatments portal ([English](#) / [French](#))
- List of drugs for exceptional importation and sale ([English/French](#))
- List of diagnostic devices for use against coronavirus (COVID-19) ([English/French](#))
- List of authorized drug clinical trials ([English/French](#))
- List of authorized device clinical trials ([English/French](#))
- Authorized medical devices for uses related to COVID-19: Overview ([English/French](#))
- List of authorized hand sanitizer products ([English/French](#))
 - As of July 6, the list is updated on Tuesdays (as opposed to daily)
- List of hard-surface disinfectants for use against coronavirus (COVID-19) ([English/French](#))
- Medical Device Respirator recalls ([English/French](#))
- Recall of certain hand sanitizers that may pose health risks ([English/French](#))
- Exceptional importation and sale of drugs in relation to COVID-19: Tier 3 drug shortages [English](#) / [French](#)

KEY CONTACTS**For any questions about this report please contact:**

Brennan Graham, COVID-19 Regulatory Response Team, Assistant Deputy Minister's Office, Health Products and Food Branch
brennan.graham@canada.ca; phone: 613-406-4725

CLINICAL TRIALS: DRUGS AND VACCINES

Drugs and vaccines for COVID-19: List of authorized clinical trials [English/French](#)

Table 1 Authorized clinical trials for drugs since January 1, 2021

Trial Name /Protocol #/control #	Title/Description	Interventions	Sites	Sponsor/ Principal Investigator / (Contact)	Authorization date
VACCINES/ PROPHYLAXIS					
CT24 CTA Control # 251972, Authorized under Clinical Trials Interim Order Amendment #1 CTA-A Control # 253276	Immunogenicity and adverse events following immunization with alternate schedules of authorized COVID-19 vaccines in Canada: MOSAIC study (Mix and match of the second cOvid-19 vaccine dose for	COVID-19 mRNA Vaccine (Pfizer- BioNTech Covid- 19 Vaccine) / mRNA-1273 SARS-CoV-2 vaccine (COVID- 19 Vaccine Moderna))+ COVID-19 Vaccine (ChAdOx1-S [recombinant]) (AstraZeneca	6 recruiting sites and 5 laboratory sites (2 of the sites are both recruiting & laboratory sites). All are Canadian.	Dalhousie University/Canadi an Immunization Research Network (CIRN)	May 5, 2021 Amendment #1 June 10, 2021

From: [REDACTED]
To: Alhaddad, Saj (HC/SC)
Cc: Hunt, Melissa (HC/SC); Rose, Jhona (HC/SC); [REDACTED]
Subject: PFIZER RESPONSE: Pfizer-BioNTech COVID-19 Vaccine Monthly Summary Safety Report letter
Date: 2021-07-23 4:20:32 PM
Attachments: 253419 Letter to MAH.pdf
Responses to MHPD Request on 12Jul2021 Password.docx

Dear Saj,
Further to the attached request from Health Canada, in advance of the filing of the next SMSR due on 15 August 2021, please find a copy of our responses.
Please note that the document is password-protected and the password is the dossier e-identifier.
The sequence will follow next week.
Sincerely,

From: Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>
Sent: Monday, July 12, 2021 9:02 PM
To: eSubmissions-CA <eSubmissions-CA@pfizer.com>
Cc: Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>; Rose, Jhona (HC/SC) <jhona.rose@canada.ca>
Subject: [EXTERNAL] Pfizer-BioNTech COVID-19 Vaccine Monthly Summary Safety Report letter control# 253419

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Please confirm receipt of this e-mail and the attached letter,

Thank you,

Saj Alhaddad

A/ Senior Regulatory Project Manager - Gestionnaire principal de projets réglementaires par intérim
Bureau of Biologics, Radiopharmaceuticals and Self-Care Products | Bureau des produits biologiques, radiopharmaceutiques et de soins autoadministrés
Marketed Health Products Directorate - (MHPD) | Direction des produits de santé commercialisés - (DPSC)

Saj.alhaddad@canada.ca

Tel : (613) 240-9514



Marketed Health Products Directorate
Address Locator # 1906A
OTTAWA, Ontario
K1A 0K9

Date: July 12, 2021

Control #: 253419

[REDACTED] Regulatory Affairs
Pfizer Canada ULC
17300 Trans-Canada Highway
KIRKLAND, Quebec
H9J 2M5

Email: ESUBMISSIONS-CA@PFIZER.COM

Dear [REDACTED]

Re: Pfizer-BioNTech COVID-19 Vaccine (tozinameran)

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3. Include in the SMSR to be submitted by August 15, 2021:
 - a. A cumulative review of the following safety topics given the seriousness of the cases including fatalities
 - b. Cardiovascular events namely, myocardial infarction, cardiac failure
 - c. Seizure (using the search criteria identified previously by HC)
 - d. Arterial Thromboembolic events (Stroke)
 - e. Venous Thromboembolic events (deep venous thrombosis [DVT] and pulmonary embolism [PE]), using: the Standard MedDRA Query (SMQ) narrow "Embolic and thrombotic events, venous"

Data should be stratified by sex, age, gender, dose 1 or dose 2 and assessed for causality using Brighton Collaboration Definition Criteria. The observed and expected analyses should be included. An analysis of Canadian cases including an assessment on causality is also requested. Once the assessment is completed the MAH should also provide a discussion on the need to update the product monograph and/or update the risk management plan.

4. Discuss the need to implement a registry with reference in the CPM for pregnant women given that cases with serious outcomes are being reported to the Canadian databases. This approach will be consistent with the other COVID vaccines currently available in Canada. .



As a general reminder, a Notification of Foreign Action should be submitted to the MHPD in accordance with subsection C.01.050 of the *Food and Drug Regulations*, when appropriate. When safety updates are implemented in other jurisdictions Health Canada would like consideration to be given by the MAH with regards to implementation of these updates in the Canadian Product Monograph. In Addition, please provide the safety reports prepared for other regulatory agencies with the MSSR submissions.

A control number has been assigned for your submission of a monthly safety report in response to this letter. The control number is **254572**. Please provide the monthly safety report before or on **July15, 2021** and include this control number in the cover letter of your response, along with a copy of this letter.

Sponsors must now submit their regulatory transactions using the Regulatory Enrolment Process (REP). By using this process, transactions in both eCTD and non-eCTD formats can be securely submitted via the Common Electronic Submissions Gateway (CESG).

Questions concerning this request should be directed to Saj Alhaddad, Acting Senior Regulatory Project Manager, BBRS, MHPD, by email at hc.mbbnhpb.rpmgpr.bpbbbsnc.sc@canada.ca.

Thank you in advance for your cooperation.

Melissa Hunt
Director
Marketed Health Products Directorate

This document has been signed electronically using the Health Canada docuBridge system. /
Ce document a été signé électroniquement à l'aide du système docuBridge de Santé Canada.

*As part of Health Canada's efforts to minimize health risk factors to Canadians while maximizing the safety provided by the regulatory system for health products, the Marketed Health Products Directorate (MHPD) has completed a comprehensive review of the Summary Monthly Safety Report (SMSR) covering the period from April 30, 2021 to May 31, 2021 for the **Pfizer-BioNTech COVID-19 Vaccine (tozinameran)** control number 253419. Please find below actions for Pfizer Canada ULC and BioNTech Manufacturing GmbH stemming from this review.*

*In accordance with the Risk Management Plan Terms and Conditions, imposed under the Interim Order Respecting the Importation, Sale and Advertising of Drugs for Use in Relation to Covid-19, Pfizer Canada ULC is required to submit monthly safety reports for the period of the Interim Order authorization. As such, you are requested to submit the monthly safety report for the period of **June 01, 2021 to June 30, 2021** including cumulative number of reports (serious and non-serious) and adverse events that occurred in Canada and globally for the **Pfizer-BioNTech COVID-19 Vaccine (tozinameran)** known to **Pfizer Canada ULC and BioNTech Manufacturing GmbH**.*

Actions for Pfizer Canada ULC and BioNTech Manufacturing GmbH stemming from the SMSR #6 review are to:

Comment 1

Facial paralysis /Bell's Palsy: From Pfizer's response to the letter issued on June 7, 2021, the following were noted: *With regards to the question on Facial paralysis /Bell's Palsy in association with the Pfizer-BioNTech COVID-19 Vaccine, the analysis on overall data in subjects reporting facial paralysis/Bell's palsy after BNT162b2 vaccination, including clinical study data, postauthorization reports and observed to expected analyses, provides inconclusive evidence of a causal association with BNT162b2. Evaluations will continue and Bell's palsy is an endpoint in Pfizer's observational surveillance studies. Updates to labeling language will be proposed if warranted upon future assessment.*

Health Canada would like to reiterate that based on the imbalance observed in the clinical trials, increase in frequency of reporting from the post-market data, and safety information captured in the EMA SmPC, EUA USPI (including Bell's Palsy) and MHRA, Health Canada's position remains the same and the need for further risk mitigation will be discussed with our pre-market colleagues.

Response 1

Comment 2

In addition, the Pfizer's response to the letter issued on June 7, 2021 noted the following: *All planned safety-related updates to the Core Data Sheet are captured in the Summary Monthly Safety Report (SMSR). As mentioned at the pre-New Drug Submission (NDS) meeting held with Health Canada (HC) on 3 June 2021, Pfizer plans on requesting a meeting with HC in the coming weeks to discuss upcoming revisions to the Product Monograph which will be filed under the second roll of the NDS CV as well as in parallel via an Interim Order Amendment.*

It is our understanding from the conversation on June 21, 2021 that Pfizer will soon submit a post-market label update to align labelling with the Core Data Sheet.

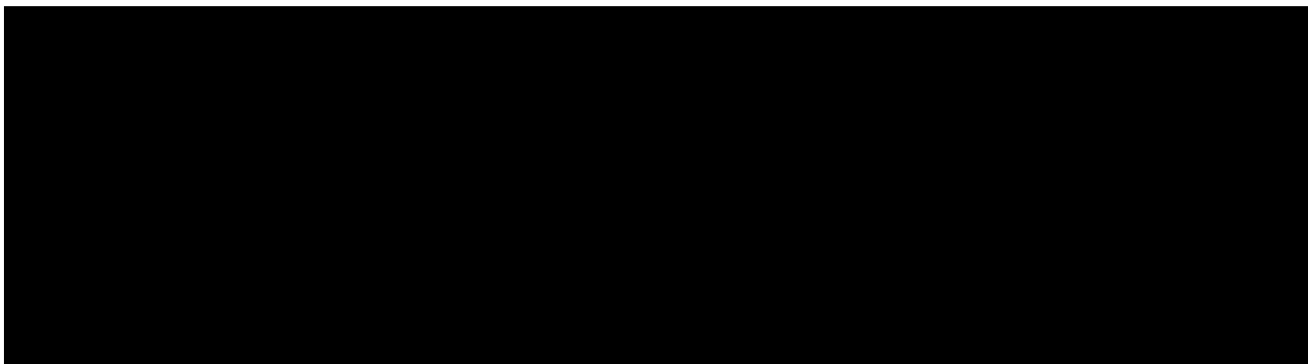
Response 2**Comment 3**

Include in the SMSR to be submitted by August 15, 2021:

- a. A cumulative review of the following safety topics given the seriousness of the cases including fatalities
- b. Cardiovascular events namely, myocardial infarction, cardiac failure
- c. Seizure (using the search criteria identified previously by HC)
- d. Arterial Thromboembolic events (Stroke)
- e. Venous Thromboembolic events (deep venous thrombosis [DVT] and pulmonary embolism [PE]), using: the Standard MedDRA Query (SMQ) narrow "Embolic and thrombotic events, venous"

Data should be stratified by sex, age, gender, dose 1 or dose 2 and assessed for causality using Brighton Collaboration Definition Criteria. The observed and expected analyses should be included. An analysis of Canadian cases including an assessment on causality is also requested. Once the assessment is completed the MAH should also provide a discussion on the need to update the product monograph and/or update the risk management plan.

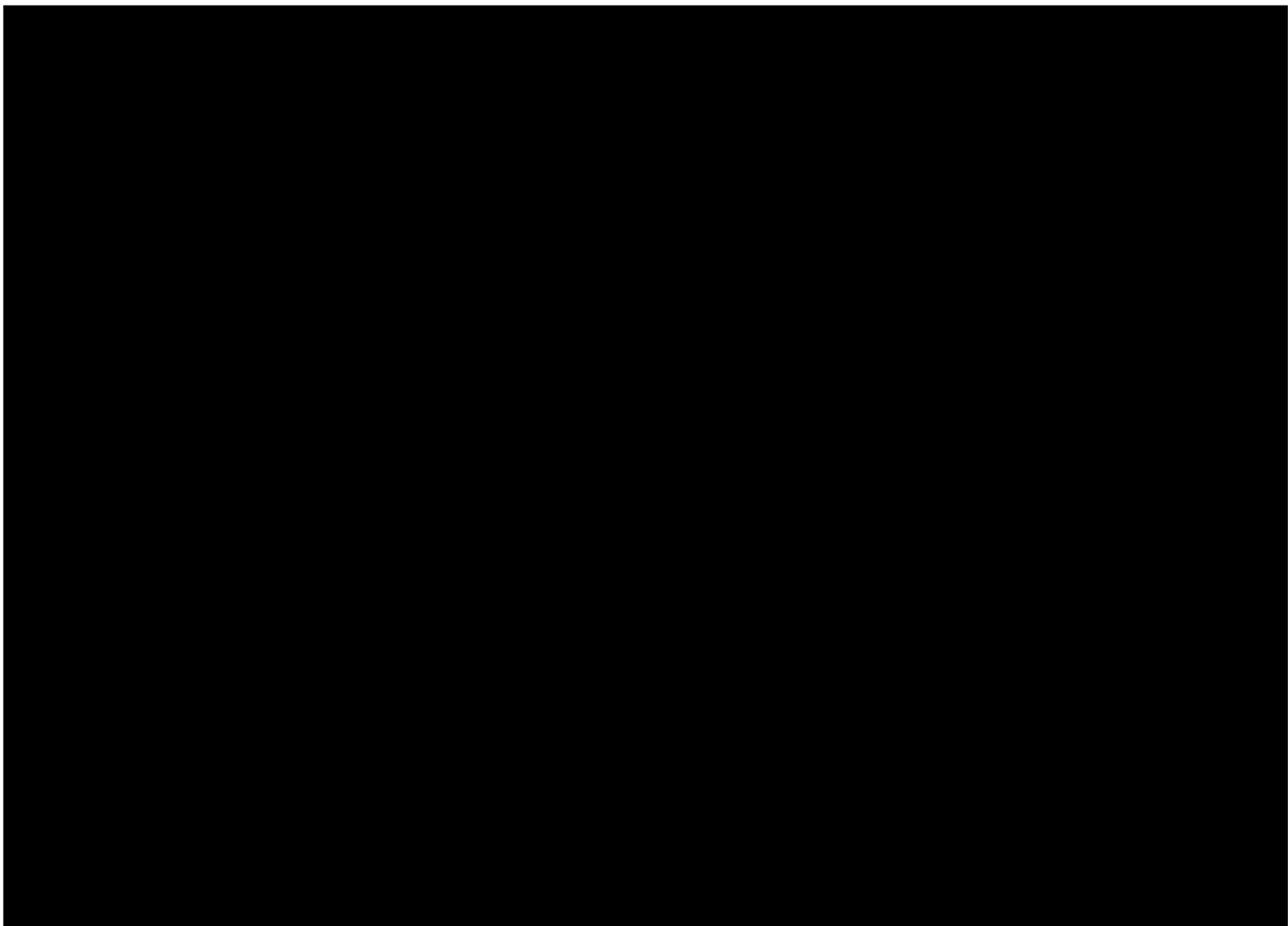
Response 3



Comment 4

Discuss the need to implement a registry with reference in the CPM for pregnant women given that cases with serious outcomes are being reported to the Canadian databases. This approach will be consistent with the other COVID vaccines currently available in Canada.

Response 4



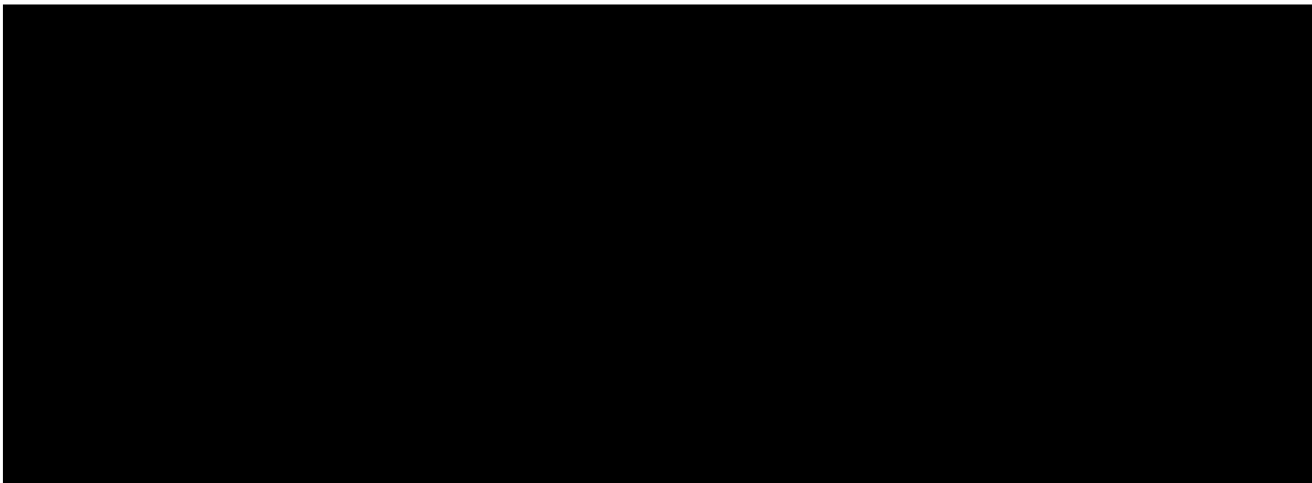


Table 1. Post-Authorization Studies for Assessing Safety of Pfizer-BioNTech COVID-19 Vaccination During Pregnancy

Protocol ID	Study Title	Data Source	Source Population and Countries	Study Status
C4591009	A Non-Interventional Post-Approval Safety Study of the Pfizer-BioNTech COVID-19 mRNA Vaccine in the United States	Sentinel System Data Research Partners	Commercial health plan enrollees from 5 data partners <i>US</i>	Planned
C4591011	Active safety surveillance of the Pfizer-BioNTech COVID-19 Vaccine in the United States Department of Defense population following Emergency Use Authorization	US Department of Defense Military Health System	US Department of Defense military and civilian personnel and their families <i>US</i>	Planned
C4591021 (formerly ACCESS/VAC4EU)	Post Conditional approval active surveillance study among individuals in Europe receiving the Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) vaccine	VAC4EU	General population <i>Netherlands, Norway, UK, Italy, and Spain</i>	Ongoing
C4591022	Pfizer-BioNTech COVID-19 Vaccine Exposure during Pregnancy: A Non-Interventional Post-Approval Safety Study of Pregnancy and Infant Outcomes in the Organization of Teratology Information Specialists (OTIS)/MotherToBaby Pregnancy Registry	OTIS/MotherToBaby Pregnancy Registry	Pregnant women aged 18 years or older participating in the pregnancy registry on or after 11 December 2020 (i.e., date FDA granted EUA for the Pfizer-BioNTech COVID-19 vaccine) <i>US and Canada</i>	Ongoing

Abbreviations: AESI, adverse event of special interest; COVID-19, Coronavirus Disease 2019; EU, European Union; EUA, Emergency Use Authorization; FDA, (US) Food and Drug Administration; mRNA, messenger ribonucleic acid; OTIS, Organization of Teratology Information Specialists; RNA, ribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; US, United States; VAC4EU, Vaccine monitoring Collaboration for Europe.

From: [Salem, Myriam \(HC/SC\)](#)
To: [Hunt, Melissa \(HC/SC\)](#)
Subject: RE: 253419_Pfizer BioNTech SMSR 6_2021-07-07_0.1.docx
Date: 2021-07-07 11:25:03 PM

Thank you!

From: Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>
Sent: 2021-07-07 6:17 PM
To: Salem, Myriam (HC/SC) <myriam.salem@canada.ca>
Cc: Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>; Rose, Jhona (HC/SC) <jhona.rose@canada.ca>
Subject: RE: 253419_Pfizer BioNTech SMSR 6_2021-07-07_0.1.docx

Thanks Myriam,

I will likely have to review it tomorrow but will as soon as I can!

Melissa

From: Salem, Myriam (HC/SC) <myriam.salem@canada.ca>
Sent: 2021-07-07 6:07 PM
To: Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>
Cc: Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>; Rose, Jhona (HC/SC) <jhona.rose@canada.ca>
Subject: 253419_Pfizer BioNTech SMSR 6_2021-07-07_0.1.docx

Hi Melissa,

Please find attached the first draft of the Pfizer MSR 6 for your review.

I apologize for the delay.

Thank you,

Myriam

From: Hunt, Melissa (HC/SC)
To: Alhaddad, Saj (HC/SC)
Cc: Rose, Jhona (HC/SC); Stothart, Tonja (HC/SC)
Subject: RE: BRDD action required: Pfizer BioNtech vaccine Memo to BRDD Control number: 251813 and 253419
Date: 2021-07-13 10:48:00 AM

Hi Saj,

Can we make sure these are also sent to Joel Raymond and Osman Ali as well?

They will likely play a role in tracking post-market requests.

Thanks!

Melissa

From: Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>

Sent: 2021-07-13 10:47 AM

To: Bouthillier, Leo (HC/SC) <leo.bouthillier@canada.ca>; Cherry, Elana (HC/SC) <elana.cherry@canada.ca>; Faraci, Maria (HC/SC) <maria.faraci@canada.ca>; Coleman, Gina (HC/SC) <gina.coleman@canada.ca>; HC.F ORA_COVID / BAR_COVID F.SC <hc.ora_covid-bar_covid.sc@canada.ca>

Cc: Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>; Rose, Jhona (HC/SC) <jhona.rose@canada.ca>; Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>; Salem, Myriam (HC/SC) <myriam.salem@canada.ca>

Subject: BRDD action required: Pfizer BioNtech vaccine Memo to BRDD Control number: 251813 and 253419

Good morning BRDD team,

The MHPD created a memo based on the review of MSR#5 and MSR#6 on facial paralysis for the PFIZER-BIONTEH COVID-19 Vaccine: [HC6-024-e243022 \(1.0\) Reg Info - Post Market Tracker](#)

Please find actions in the memo for BRDD's immediate action. Should you require a meeting to discuss this, please let us know.

Regards,

Saj Alhaddad

A/ Senior Regulatory Project Manager - Gestionnaire principal de projets réglementaires par intérim
 Bureau of Biologics, Radiopharmaceuticals and Self-Care Products | Bureau des produits
 biologiques, radiopharmaceutiques et de soins autoadministrés
 Marketed Health Products Directorate - (MHPD) | Direction des produits de santé commercialisés -
 (DPSC)

Saj.alhaddad@canada.ca

Tel : (613) 240-9514

From: Coleman, Gina (HC/SC)
To: Rose, Jhona (HC/SC); Salem, Myriam (HC/SC); Alhaddad, Saj (HC/SC); Bouthillier, Leo (HC/SC); Cherry, Elana (HC/SC); Faraci, Maria (HC/SC); HC.F ORA_COVID / BAR_COVID F.SC; Raymond, Joel (HC/SC); Ali, Osman (HC/SC)
Cc: Hunt, Melissa (HC/SC); Stothart, Tonja (HC/SC)
Subject: RE: BRDD action required: Pfizer BioNtech vaccine Memo to BRDD Control number: 251813 and 253419
Date: 2021-07-13 11:25:50 AM

Thank you Jhona.

As for item 3, it was recommended by MHPD! If MHPD does not want it, I have no problem removing it.

Gina

From: Rose, Jhona (HC/SC) <jhona.rose@canada.ca>

Sent: 2021-07-13 11:24 AM

To: Salem, Myriam (HC/SC) <myriam.salem@canada.ca>; Coleman, Gina (HC/SC) <gina.coleman@canada.ca>; Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>; Bouthillier, Leo (HC/SC) <leo.bouthillier@canada.ca>; Cherry, Elana (HC/SC) <elana.cherry@canada.ca>; Faraci, Maria (HC/SC) <maria.faraci@canada.ca>; HC.F ORA_COVID / BAR_COVID F.SC <hc.ora_covid-bar_covid.sc@canada.ca>; Raymond, Joel (HC/SC) <joel.raymond@canada.ca>; Ali, Osman (HC/SC) <osman.ali@canada.ca>

Cc: Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>; Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>

Subject: RE: BRDD action required: Pfizer BioNtech vaccine Memo to BRDD Control number: 251813 and 253419

Hello everyone,

Agree with the timeline. Added a few texts below (highlighted)

Also, sorry just one question about item 3. Just wondering if this is needed.

Thank you.

Jhona

From: Salem, Myriam (HC/SC) <myriam.salem@canada.ca>

Sent: 2021-07-13 11:12 AM

To: Coleman, Gina (HC/SC) <gina.coleman@canada.ca>; Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>; Bouthillier, Leo (HC/SC) <leo.bouthillier@canada.ca>; Cherry, Elana (HC/SC) <elana.cherry@canada.ca>; Faraci, Maria (HC/SC) <maria.faraci@canada.ca>; HC.F ORA_COVID / BAR_COVID F.SC <hc.ora_covid-bar_covid.sc@canada.ca>; Raymond, Joel (HC/SC) <joel.raymond@canada.ca>; Ali, Osman (HC/SC) <osman.ali@canada.ca>

Cc: Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>; Rose, Jhona (HC/SC) <jhona.rose@canada.ca>; Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>

Subject: RE: BRDD action required: Pfizer BioNtech vaccine Memo to BRDD Control number: 251813 and 253419

Hi Gina,

RSI is the Reference Safety Information; however, I have changed it below to CDS (Core Data Sheet) in red.

Thank you,

Myriam

From: Coleman, Gina (HC/SC) <gina.coleman@canada.ca>

Sent: 2021-07-13 11:07 AM

To: Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>; Bouthillier, Leo (HC/SC) <leo.bouthillier@canada.ca>; Cherry, Elana (HC/SC) <elana.cherry@canada.ca>; Faraci, Maria (HC/SC) <maria.faraci@canada.ca>; HC.F ORA_COVID / BAR_COVID F.SC <hc.ora_covid_bar_covid.sc@canada.ca>; Raymond, Joel (HC/SC) <joel.raymond@canada.ca>; Ali, Osman (HC/SC) <osman.ali@canada.ca>

Cc: Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>; Rose, Jhona (HC/SC) <jhona.rose@canada.ca>; Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>; Salem, Myriam (HC/SC) <myriam.salem@canada.ca>

Subject: RE: BRDD action required: Pfizer BioNtech vaccine Memo to BRDD Control number: 251813 and 253419

Hi Saj,

I don't think we need a meeting for this, the MHPD memo is very clear.

I suggest the following wording for the clarifax, however comments are welcome. I'm afraid I don't know what RSI means (in the 4th request).

I would give them one week to submit the Post-authorization change.

1. Please add acute facial paralysis Under section 8.2 Clinical Trial Adverse Reactions/Unsolicited Adverse Events/Serious Adverse Events

Through the clinical trial safety follow-up period to 14 November 2020, acute peripheral facial paralysis (or palsy) was reported by four participants in the COVID-19 mRNA Vaccine group. Onset was Day 37 after Dose 1 (participant did not receive Dose 2) and Days 3, 9, and 48 after Dose 2. No cases of acute peripheral facial paralysis (or palsy) were reported in the placebo group.

As frequency has not been assessed in Canada, the addition of these events as Unknown frequency is recommended:

2. The addition of facial paralysis/Bell's Palsy under section 8.3 Post-Market Adverse Reactions Nervous System Disorders: facial paralysis/Bell's Palsy

3. The addition of an Unknown frequency paragraph in the Patient Medication Information under:

What are possible side effects from using Pfizer-BioNTech COVID-19 Vaccine? Like all vaccines, Pfizer-BioNTech COVID-19 Vaccine can cause side effects.

Side effects may occur at the following frequencies:

Unknown:

Facial paralysis/Bell's Palsy

4. We also request that the MAH update the Canadian Product Monograph to align with the Company Data Sheet (CDS) including but not limited to the following events Asthenia, Lethargy, Decreased appetite, Hyperhidrosis, Night sweats, Paresthesia, tachycardia and hypoesthesia.

Thanks,

Gina

From: Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>

Sent: 2021-07-13 10:49 AM

To: Bouthillier, Leo (HC/SC) <leo.bouthillier@canada.ca>; Cherry, Elana (HC/SC) <elana.cherry@canada.ca>; Faraci, Maria (HC/SC) <maria.faraci@canada.ca>; Coleman, Gina (HC/SC) <gina.coleman@canada.ca>; HC.F ORA_COVID / BAR_COVID F.SC <hc.ora_covid_bar_covid.sc@canada.ca>

bar_covid.sc@canada.ca; Raymond, Joel (HC/SC) <joel.raymond@canada.ca>; Ali, Osman (HC/SC) <osman.ali@canada.ca>

Cc: Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>; Rose, Jhona (HC/SC) <jhona.rose@canada.ca>; Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>; Salem, Myriam (HC/SC) <myriam.salem@canada.ca>

Subject: RE: BRDD action required: Pfizer BioNtech vaccine Memo to BRDD Control number: 251813 and 253419

Looping BRDD risk team in as well. Saj

From: Alhaddad, Saj (HC/SC)

Sent: 2021-07-13 10:47 AM

To: Bouthillier, Leo (HC/SC) <leo.bouthillier@canada.ca>; Cherry, Elana (HC/SC) <elana.cherry@canada.ca>; Faraci, Maria (HC/SC) <maria.faraci@canada.ca>; Coleman, Gina (HC/SC) <gina.coleman@canada.ca>; HC.F ORA_COVID / BAR_COVID F.SC <hc.ora_covid-bar_covid.sc@canada.ca>

Cc: Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>; Rose, Jhona (HC/SC) <jhona.rose@canada.ca>; Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>; Salem, Myriam (HC/SC) <myriam.salem@canada.ca>

Subject: BRDD action required: Pfizer BioNtech vaccine Memo to BRDD Control number: 251813 and 253419

Good morning BRDD team,

The MHPD created a memo based on the review of MSR#5 and MSR#6 on facial paralysis for the PFIZER-BIONTEH COVID-19 Vaccine: [HC6-024-e243022 \(1.0\) Reg Info - Post Market Tracker](#)
Please find actions in the memo for BRDD's immediate action. Should you require a meeting to discuss this, please let us know.

Regards,

Saj Alhaddad

A/ Senior Regulatory Project Manager - Gestionnaire principal de projets réglementaires par intérim
Bureau of Biologics, Radiopharmaceuticals and Self-Care Products | Bureau des produits
biologiques, radiopharmaceutiques et de soins autoadministrés
Marketed Health Products Directorate - (MHPD) | Direction des produits de santé commercialisés -
(DPSC)

Saj.alhaddad@canada.ca

Tel : (613) 240-9514

From: Rose, Jhona (HC/SC)
To: Salem, Myriam (HC/SC); Stothart, Tonja (HC/SC); Hunt, Melissa (HC/SC); Alhaddad, Saj (HC/SC)
Subject: FW: COVID-19: Interim Order Application Amendment for Pfizer-BioNTech COVID-19 Vaccine, control # 254768 - PM 6 months safety update
Date: 2021-07-15 8:09:30 PM

Hello Everyone,
 Please see below.
 Highlighted below for our review and comments.
 Saj-please collate the comments/suggestions.
 Thank you.
 Jhona

From: Eassa, Samar (HC/SC) <samar.eassa@canada.ca>
Sent: 2021-07-15 5:43 PM
To: Lourenco, Celia (HC/SC) <celia.lourenco@canada.ca>; Hardy, Stephanie (HC/SC) <stephanie.hardy@canada.ca>; Pham, Co (HC/SC) <co.pham@canada.ca>; Bouthillier, Leo (HC/SC) <leo.bouthillier@canada.ca>; Cherry, Elana (HC/SC) <elana.cherry@canada.ca>; Coleman, Gina (HC/SC) <gina.coleman@canada.ca>; Cao, Ming Yu (HC/SC) <mingyu.cao@canada.ca>; Zhang, Judy (HC/SC) <judy.zhang@canada.ca>; Blahoianu, Maria (HC/SC) <maria.blahoianu@canada.ca>
Cc: HC.F ORA_COVID / BAR_COVID F.SC <hc.ora_covid-bar_covid.sc@canada.ca>; HC.F BBRs COVID Vaccines Team / Equipe Vaccins COVID du BBRA F.SC <hc.bbrscovidvaccinesteam-equipevaccinscoviddubbra.sc@canada.ca>; Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>
Subject: COVID-19: Interim Order Application Amendment for Pfizer-BioNTech COVID-19 Vaccine, control # 254768 - PM 6 months safety update

Hello,

The following submission is ready for review:

Brand Name: Pfizer-BioNTech COVID-19 Vaccine **control#:** 254768

Link to sequence on docuBridge: [HC6-024-e243022 \(0139\) Biologic Dossier](#)

Link to screening report: N/A

Target Date:

- N/A

Submission Notes:

This is a Level II Safety SNDS, to propose the following:

- 1- 6-month update to the C4591001 CSR. The submission addresses Clinical Conditions # 1 and 2 of the Interim Order Authorization for Pfizer-BioNTech COVID-19 Vaccine initial application Terms and Conditions control # 244906.
- 2- Response to Post Decision Letter issued under COV19A control # 252524.
- 3- Addition of a warning regarding vaccination stress related events, in response to address MHPD request for PM update, under PSUR –PV control #253419

The following is included in this sequence:

- [Response to Post decision Letter](#) issued under COV19A control # 252524.
- [Draft meeting minutes](#) for the meeting held for PM discussion held on June 21, 2021, under PSUR control # 253419 is included under this amendment, please forward your comments to the minutes if any.

- General Note to Reviewer
- Clean and annotated PM copies
- Second language PM copy
- Non-Canadian Labeling: EUA-USPI
- Company Core Data Sheet (CCDS) dated May 19, 2021 updated with the 6 months Safety proposed update
- Clinical Overview BLA/Vaccine stress related responses
- Clinical study reports for C4591001

The draft copy for the proposed PM will be rolled into Pfizer NDS CV for COMIRNATRY, control # 252736. In the rolling sequence planned for submission on July 16, 2021.

Best regards,

Samar

From: Eassa, Samar (HC/SC)
To: Zhang, Judy (HC/SC); Lourenco, Celia (HC/SC); Hardy, Stephanie (HC/SC); Pham, Co (HC/SC); Bouthillier, Leo (HC/SC); Cherry, Elana (HC/SC); Coleman, Gina (HC/SC); Blahoianu, Maria (HC/SC)
Cc: HC.F ORA_COVID / BAR_COVID F.SC; HC.F BBRS COVID Vaccines Team / Equipe Vaccins COVID du BBRA F.SC; Alhaddad, Saj (HC/SC)
Subject: RE: COVID-19: Interim Order Application Amendment for Pfizer-BioNTech COVID-19 Vaccine, control # 254768 - PM 6 months safety update
Date: 2021-07-17 11:22:33 AM

Good morning Judy,

- 1- The below submission is an **Interim Order (IO) Application Amendment**, submitted under the IO for expedited review of the PM safety changes. The proposed change is comparable to a level II safety SNDS, when assessed against the submissions filed under Division 8. However, the below submission is **not** a SNDS, and **not** a rolling sequence under the NDS CV. As such it is given a separate control # 254768.
kindly note that till the expiration date of the Interim Order (IO) on September 16, 2021, further proposed changes will be submitted under 2 platforms: 1- The Interim Order (IO) as amendments, which will be assigned new control number, 2- the NDS CV (control # 252736) which captures the work done and changes reviewed under the IO until it expires.
- 2- Sequence #0139, is correctly uploaded in db under control # 254768, since it is a standalone IO amendment.
- 3- The same information submitted under this IO amendment **will be rolled** under the NDS CV for completion, as previously discussed with Pfizer, that all information submitted under the IO should be submitted in parallel under the transition NDS CV control # 252736. However, please note that Pfizer is facing technical difficulties with the rolling sequence that includes the below information, and it has **not** been submitted, through the gate way, yet.
- 4- Since this is a safety update to the PM, then review for this amendment should be completed and a decision should be issued **before September 16, 2021**.

Hope this addresses your query, please let me know if you will need further clarifications,

Best regards,

Samar

From: Zhang, Judy (HC/SC) <judy.zhang@canada.ca>

Sent: Saturday, July 17, 2021 8:05 AM

To: Eassa, Samar (HC/SC) <samar.eassa@canada.ca>; Lourenco, Celia (HC/SC) <celia.lourenco@canada.ca>; Hardy, Stephanie (HC/SC) <stephanie.hardy@canada.ca>; Pham, Co (HC/SC) <co.pham@canada.ca>; Bouthillier, Leo (HC/SC) <leo.bouthillier@canada.ca>; Cherry, Elana (HC/SC) <elana.cherry@canada.ca>; Coleman, Gina (HC/SC) <gina.coleman@canada.ca>; Blahoianu, Maria (HC/SC) <maria.blahoianu@canada.ca>

Cc: HC.F ORA_COVID / BAR_COVID F.SC <hc.ora_covid-bar_covid.sc@canada.ca>; HC.F BBRS COVID Vaccines Team / Equipe Vaccins COVID du BBRA F.SC <hc.bbbscovidvaccinesteam-equipevaccinscoviddubbra.sc@canada.ca>; Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>

Subject: RE: COVID-19: Interim Order Application Amendment for Pfizer-BioNTech COVID-19 Vaccine, control # 254768 - PM 6 months safety update

Hi Samar,

Thank you for the email.

Just for clarification, as indicated in this email (below):

- “This is a Level II Safety SNDS” (control #254768)
- “The draft copy for the proposed PM will be rolled into Pfizer NDS CV for COMIRNATRY, control # 252736. In the rolling sequence planned for submission on July 16, 2021”.

However, the information submitted in dB (SNDS, #254768) sequence 0139, including the “proposed PM” corresponds to NDS-CV rolling submission plan (control # 252736).

Just wondering, why there are 2 different control numbers? Is the submission a SNDS or a NDS-cv?

Please clarify. Thank you!

This is an email received on July 14:

Clinical:

Today (July 14)

- Sequence 0139: PM safety update – Warning re: vaccination stress related events and 6-month safety update (further to PM consultation meeting of 21 June 2021)

All amendments are submitted under the IO, and rolled under the NDS CV in parallel.

Judy

From: Eassa, Samar (HC/SC) <samar.eassa@canada.ca>

Sent: 2021-07-15 5:43 PM

To: Lourenco, Celia (HC/SC) <celia.lourenco@canada.ca>; Hardy, Stephanie (HC/SC) <stephanie.hardy@canada.ca>; Pham, Co (HC/SC) <co.pham@canada.ca>; Bouthillier, Leo (HC/SC) <leo.bouthillier@canada.ca>; Cherry, Elana (HC/SC) <elana.cherry@canada.ca>; Coleman, Gina (HC/SC) <gina.coleman@canada.ca>; Cao, Ming Yu (HC/SC) <mingyu.cao@canada.ca>; Zhang, Judy (HC/SC) <judy.zhang@canada.ca>; Blahoianu, Maria (HC/SC) <maria.blahoianu@canada.ca>

Cc: HC.F ORA_COVID / BAR_COVID F.SC <hc.ora_covid-bar_covid.sc@canada.ca>; HC.F BBRS COVID Vaccines Team / Equipe Vaccins COVID du BBRA F.SC <hc.bbrcscovidvaccinesteam-equipevaccinscovidubbra.sc@canada.ca>; Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>

Subject: COVID-19: Interim Order Application Amendment for Pfizer-BioNTech COVID-19 Vaccine, control # 254768 - PM 6 months safety update

Hello,

The following submission is ready for review:

Brand Name: Pfizer-BioNTech COVID-19 Vaccine **control#:** 254768

Link to sequence on docuBridge: [HC6-024-e243022 \(0139\) Biologic Dossier](#)

Link to screening report: N/A

Target Date:

- N/A

Submission Notes:

This is a Level II Safety SNDS, to propose the following:

- 1-6-month update to the C4591001 CSR. The submission addresses Clinical Conditions # 1 and 2 of the Interim Order Authorization for Pfizer-BioNTech COVID-19 Vaccine initial application Terms and Conditions control # 244906.

2- Response to Post Decision Letter issued under COV19A control # 252524.

3- Addition of a warning regarding vaccination stress related events, in response to address MHPD request for PM update, under PSUR –PV control #253419

The following is included in this sequence:

- Response to Post decision Letter issued under COV19A control # 252524.
- Draft meeting minutes for the meeting held for PM discussion held on June 21, 2021, under PSUR control # 253419 is included under this amendment, please forward your comments to the minutes if any.
- General Note to Reviewer
- Clean and annotated PM copies
- Second language PM copy
- Non-Canadian Labeling: EUA-USPI
- Company Core Data Sheet (CCDS) dated May 19, 2021 updated with the 6 months Safety proposed update
- Clinical Overview BLA/Vaccine stress related responses
- Clinical study reports for C4591001

The draft copy for the proposed PM will be rolled into Pfizer NDS CV for COMIRNATRY, control # 252736. In the rolling sequence planned for submission on July 16, 2021.

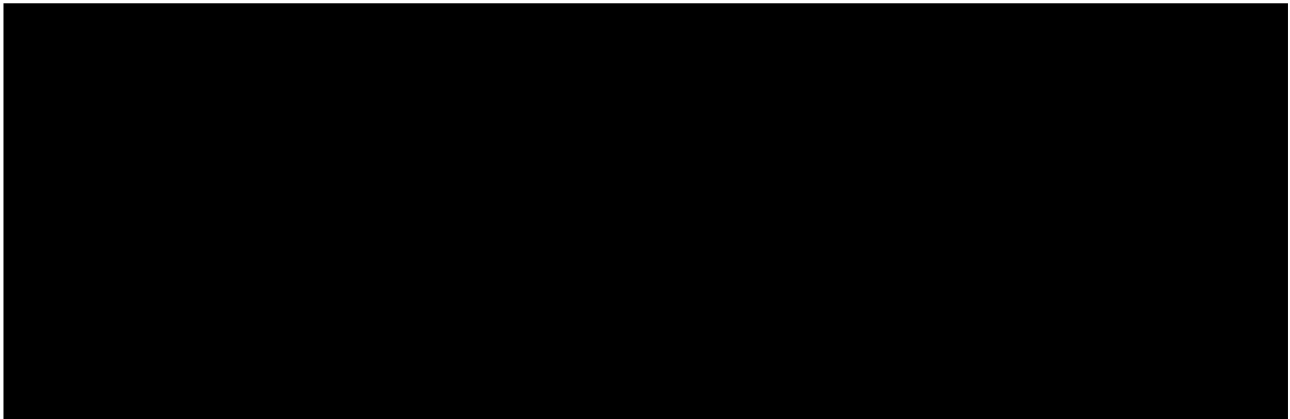
Best regards,

Samar

Comment 1

In a future application amendment, incorporate the following update under Section 8.1 “Adverse Reaction Overview”, Page 13 of the Product Monograph (PM):

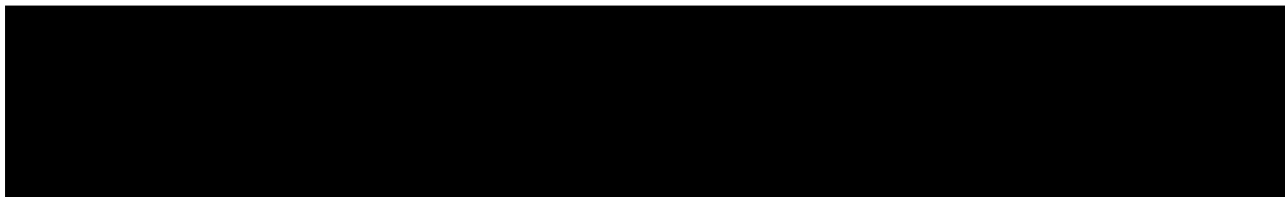
“Adverse reactions at any dose within 7 days in adolescents 12 to 15 years of age included pain at the injection site (90.5%), fatigue (77.5%), headache (75.5%), chills (49.2%), muscle pain (42.2%), fever (24.3%), joint pain (20.2%), injection site swelling (9.2%), injection site redness (8.6%), lymphadenopathy (0.8%), and nausea (0.4%)”.

Response

Comment 2

In the French PM revise the following paragraph under section 11 “Conservation, stabilité et Mise au rebut”, Page 25 as follows for clarity:

« Les données accumulées viennent appuyer le transport d’une ou plusieurs fiole(s) décongelée(s) entre 2 et 8 °C (35 et 46 °F), pendant une période maximale de 12 heures. Toutes les heures consacrées au transport à une température de 2 à 8 °C (35 à 46 °F) devront toutefois être déduites de la période maximale de 1 mois de conservation entre 2 et 8 °C (35 et 46 °F). »

Response

Comment 3

Provide the revised Shipping and Handling Guidelines and S.T.E.P.S. leaflet incorporating the approved storage condition update, to be posted to the Health Canada portal by June 1, 2021.

Response

**Pfizer-BioNTech COVID-19 Vaccine (BNT162/PF-07302048)
Product Monograph Consultation Meeting of 21 June 2021**

Draft Minutes

MEETING DATE: 21 June 2021 (11:30 AM-12:00 PM)

**MEETING
LOCATION:** WEBEX

ATTENDEES:

HEALTH CANADA **Melissa Hunt** – Director, COVID Response Team, Bureau of Biologics, Radiopharmaceuticals and Self-Care Products, Marketed Health Products Directorate (CRT-BBRS-MHPD)
Jhona Rose – A/Manager, CRT-BBRS-MHPD
Dr. Tonja Stothart – Medical Manager, CRT-BBRS-MHPD
Myriam Salem – Senior Scientific Evaluator, CRT-BBRS-MHPD
Saj Alhaddad – Acting Senior Regulatory Project Manager, CRT-BBRS-MHPD
Dr. Leo Bouthillier – Director, Centre for Evaluation of Radiopharmaceuticals and Biotherapeutic, Biologics and Radiopharmaceutical Drugs Directorate (CERB-BRDD)
Maria Blahoianu – A/ Manager, Clinical Evaluation Division – Vaccines BRDD
Samar Eassa - Senior Regulatory Affairs Officer, Office of Regulatory Affairs BRDD
Vincent Panetta - Regulatory Affairs Supervisor, Office of Regulatory Affairs BRDD

PFIZER CANADA [REDACTED] [REDACTED] Regulatory Affairs, Pfizer Canada
[REDACTED] - Associate Director, Regulatory Affairs, Pfizer Canada

INTRODUCTION

Pfizer thanked HC for the opportunity to meet and noted that the objective of the meeting was to discuss upcoming changes to the Product Monograph (PM) for Pfizer-BioNTech COVID-19 Vaccine and seek HC feedback on the filing approach.

DISCUSSION and QUESTIONS

Pfizer stated that, following the recent filing of the NDS-CV, one of the elements to be submitted in the upcoming 2nd roll (planned for 16 June 2021) is the updated Product Monograph. Pfizer indicated that there have been recent updates to the Core Data Sheet as well as revisions to the US EUA Label and to the EU SmPC (currently under review in the US and EU). Given the current unique situation, with having an active Interim Order and the NDS-CV under review, Pfizer requested HC feedback as to how to file the planned changes to the Pfizer-BioNTech COVID-19 Vaccine PM.

Pfizer provided an overview of the safety-related revisions to the PM that were planned to be filed in the 2nd roll of the NDS-CV:

- Further to the 6-month update to the Clinical Study Report (CSR) filed in the NDS-CV, there are numerous revisions to be made to the Product Monograph. From a Safety standpoint, based on the 6-month update, there are a few adverse events to be added. These were the AEs noted in the MHPD e-mail request dated 7 June 2021, i.e. *Asthenia, Lethargy, Decreased appetite, Hyperhidrosis, Night sweats*. Although these are new AEs to be added, all were reported in $\leq 0.3\%$ of subjects.
- Based also on the 6-month update there will be revisions to the local and systemic AE tables. The revisions are not substantial and simply consist of minor updates to the numbers previously reported in the tables.
- Not based on the 6-month update but rather based on additional post-marketing data, there will be an update under WARNING AND PRECAUTIONS to include information on stress-related responses associated with the process of vaccination.
- New analyses in 200 stable HIV patients will also be included in the PM.

Pfizer asked HC if they would expect that the Interim Order (IO) PM also be updated and if yes, what extent of information should be filed in the IO PM. Pfizer added that the intent was not to include the efficacy analysis from the 6-month update in the IO PM.

HC confirmed that from an overarching principle we should not wait to include safety updates in the PM and these should be filed as soon as possible to ensure that the safety information in the PM is aligned with other International labels and to avoid discrepancies with other regions. Therefore, since the NDS-CV is only planned to be approved in mid-September, HC's preference would be that the safety-related changes also be filed to the IO PM.

HC noted that Bell's palsy and/or facial swelling are included in the US EUA label as well as the SmPC but are not captured in the current PM. As indicated in Pfizer's response to the MHPD's request of 7 June 2021 (response filed with Summary Monthly Safety Report on 14 June 2021), the analysis on overall data in subjects reporting facial paralysis/Bell's palsy after BNT162b2 vaccination, provided inconclusive evidence of a causal association with BNT162b2. Therefore, Pfizer stated that information on Bell's palsy and facial swelling was not captured in the Core Data Sheet. Pfizer explained that additions in the US and EU were based on specific requests from FDA and EMA. Should HC require that Pfizer add Bell's palsy and/or facial swelling in the PM, a formal request from HC would be required. HC concurred and stated that they will be reviewing the information in the latest SMSR to determine if Bell's palsy and/or facial swelling needs to be added in the PM.

In summary, Pfizer indicated that based on HC's feedback, the 6-month CSR will be submitted to the IO but Pfizer will only focus on the safety updates to the PM for the IO. Pfizer noted that the plan is to file an IO Amendment providing for the PM revisions by mid-July, potentially a few days prior to the NDS-CV 2nd roll. Pfizer re-iterated that all the AEs to be added are non-serious and all reported in $\leq 0.3\%$ of individuals. Pfizer added that these AEs are being included in the PM simply in the context of the COVID-19 vaccine and would normally not meet the criteria to be added to the PM based on HC's PM Guidance.

In conclusion Pfizer thanked HC for their input and agreed to keep HC informed of any additional updates or changes to the plan.

1.0.7 General Note to Reviewer

Product Monograph Safety Update

The purpose of this amendment is to request authorization of a safety update to the Pfizer-BioNTech COVID-19 Vaccine Product Monograph for

- the addition of a warning regarding vaccination stress related events, and
- an update to the existing safety information in individuals 16 years of age and older based on the 6-month update to the C4591001 clinical study report (CSR).

These safety updates are further to Pfizer's response of 14 June 2021 to the MHPD request dated 7 June 2021 (Dossier ID e243022, Sequence 0133) and were the focus of the Product Monograph (PM) consultation meeting held on 21 June 2021. In the email dated 22 June 2021, Health Canada had agreed that the draft minutes of the PM consultation meeting could be provided in this amendment and thus they are enclosed. As indicated by Pfizer during the PM consultation meeting, these safety revisions are reflected in the draft COMIRNATY PM to be filed in NDS Roll 2 under Dossier ID e252736 on 16 July 2021.

The addition of the warning regarding vaccination stress related events is supported by the enclosed 2.5 Clinical Overview – Vaccine Stress Related Responses. This warning includes a description of the symptoms that may be seen with a stress related response, including paresthesia (denoted as 'tingling sensations' in the Product Monograph).

The C459001 6-month update CSR has already been submitted under the COMIRNATY NDS Roll 1 (Dossier ID e252736, Sequence 0000), and is now also being filed under the Interim Order Authorization for Pfizer-BioNTech COVID-19 Vaccine. This 6-month update is the source of new adverse events that have been added to the Core Data Sheet and Emergency Use Authorization United States Prescribing Information (EUA USPI), i.e., asthenia, lethargy, decreased appetite, hyperhidrosis, night sweats. Based on the 6-month CSR, the existing patient exposure numbers and incidences for adverse reactions have also been updated for individuals 16 years of age and older. Please note that although it was stated at the PM consultation meeting that new analyses in 200 stable HIV patients would be included in the PM, a decision was taken not to include this new information at this time, and to focus on updating the existing information. These analyses in HIV patients are included in the draft COMIRNATY PM being filed in parallel.

The revised PM included in this amendment reflects the revisions requested in Health Canada's Post-Decision Letter dated 25 May 2021 (Control No. 252524). Please refer to Pfizer's response to this Post-Decision Letter, provided in this sequence for further information.

In the United States, these labeling changes were filed as amendments to the EUA and they are currently under review by the Food and Drug Administration. Consequently, these changes are not reflected in the current approved EUA USPI provided for reference in Module 1.3.3.

The current approved Core Data Sheet is also provided for reference in Module 1.6.2.

Fulfilling Terms and Conditions

As requested by Health Canada, the C4591001 6-month update CSR is being filed in support of this PM safety update. However, this CSR is also being submitted in fulfillment of Clinical Conditions # 1 and 2 of the Interim Order Authorization Terms and Conditions (Control No. 244906), i.e.,

1. *Provide the 6-month safety update for subjects of the Phase 1, Phase 2 and Phase 2/3 study, when the 6-month safety update will be available for the 6000 study subjects of Phase 2/3 study.*
2. *The sponsor plans to maintain the participants in the ongoing Phase 3 Study- C4591001 as originally randomized (for as long as possible) to accumulate 6 months of safety follow-up data after Dose 2. The study team responsible for study conduct would remain blinded to individual participant randomization until this time. Provide results obtained during this period of time (up to 6 months after Dose 2) regarding the vaccine efficacy from Phase 3 and immunogenicity data from Phase 2 of Study- C4591001.*

As noted above, this C459001 6-month update CSR (and the associated updated Module 2 clinical summary documents, i.e., 2.5 Clinical Overview, 2.7.3 Summary of Clinical Efficacy and 2.7.4 Summary of Clinical Safety) have already been submitted under the COMIRNATY NDS Roll 1 and are now being filed under the Interim Order Authorization for Pfizer-BioNTech COVID-19 Vaccine.

From: Coleman, Gina (HC/SC)
To: Eassa, Samar (HC/SC); Ali, Osman (HC/SC); Bouthillier, Leo (HC/SC); Raymond, Joel (HC/SC); BRDD.Risk / risque.DMBR (HC/SC); Salem, Myriam (HC/SC)
Cc: Rose, Jhona (HC/SC); Alhaddad, Saj (HC/SC); Cherry, Elana (HC/SC); Faraci, Maria (HC/SC); HC.F ORA COVID / BAR COVID F.SC; Hunt, Melissa (HC/SC); Stothart, Tonja (HC/SC); Panetta, Vincent (HC/SC)
Subject: RE: FYI - Advisement Letter issued for Pfizer BioNtech Covid19 vaccine [CTRL # 254700]
Date: 2021-07-19 10:10:05 AM

It's OK with me.

Thanks,

Gina

From: Eassa, Samar (HC/SC) <samar.eassa@canada.ca>

Sent: 2021-07-19 10:03 AM

To: Ali, Osman (HC/SC) <osman.ali@canada.ca>; Bouthillier, Leo (HC/SC) <leo.bouthillier@canada.ca>; Coleman, Gina (HC/SC) <gina.coleman@canada.ca>; Raymond, Joel (HC/SC) <joel.raymond@canada.ca>; BRDD.Risk / risque.DMBR (HC/SC) <hc.brdd.risk-
risque.dmb.r.sc@canada.ca>; Salem, Myriam (HC/SC) <myriam.salem@canada.ca>

Cc: Rose, Jhona (HC/SC) <jhona.rose@canada.ca>; Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>; Cherry, Elana (HC/SC) <elana.cherry@canada.ca>; Faraci, Maria (HC/SC) <maria.faraci@canada.ca>; HC.F ORA_COVID / BAR_COVID F.SC <hc.ora_covid-
bar_covid.sc@canada.ca>; Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>; Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>; Panetta, Vincent (HC/SC) <vincent.panetta@canada.ca>

Subject: RE: FYI - Advisement Letter issued for Pfizer BioNtech Covid19 vaccine [CTRL # 254700]

Dear all,

The sponsor is requesting a 2 days' extension to the response due date for the below Advisement Letter to be provided on **Friday, July, 23, 2021**.

Please let us know if this will be acceptable.

Best regards,

Samar

From: Ali, Osman (HC/SC) <osman.ali@canada.ca>

Sent: Wednesday, July 14, 2021 11:39 AM

To: Bouthillier, Leo (HC/SC) <leo.bouthillier@canada.ca>; Coleman, Gina (HC/SC) <gina.coleman@canada.ca>; Raymond, Joel (HC/SC) <joel.raymond@canada.ca>; BRDD.Risk / risque.DMBR (HC/SC) <hc.brdd.risk-
risque.dmb.r.sc@canada.ca>; Salem, Myriam (HC/SC) <myriam.salem@canada.ca>

Cc: Rose, Jhona (HC/SC) <jhona.rose@canada.ca>; Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>; Cherry, Elana (HC/SC) <elana.cherry@canada.ca>; Faraci, Maria (HC/SC) <maria.faraci@canada.ca>; HC.F ORA_COVID / BAR_COVID F.SC <hc.ora_covid-
bar_covid.sc@canada.ca>; Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>; Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>; Panetta, Vincent (HC/SC) <vincent.panetta@canada.ca>

Subject: FYI - Advisement Letter issued for Pfizer BioNtech Covid19 vaccine [CTRL # 254700]

Hi All,

The advisement letter to PFIZER - BioNtech for their COVID19 vaccine [CTRL # 254700] has been signed and issued on July 14th, 2021.

The target date for response is July 21, 2021.

Here is the link to the email sent to the sponsor with the advisement letter attached:

HC6-024-e243022 (1.0) Reg Info - Health Product

Let me know if there are any questions or concerns,

Kind regards,

Osman Ali

From: Bouthillier, Leo (HC/SC) <leo.bouthillier@canada.ca>

Sent: 2021-07-13 4:51 PM

To: Coleman, Gina (HC/SC) <gina.coleman@canada.ca>; Raymond, Joel (HC/SC) <joel.raymond@canada.ca>; BRDD.Risk / risque.DMBR (HC/SC) <[hc.brdd.risk-
risque.dnbr.sc@canada.ca](mailto:hc.brdd.risk-risque.dnbr.sc@canada.ca)>; Salem, Myriam (HC/SC) <myriam.salem@canada.ca>

Cc: Rose, Jhona (HC/SC) <jhona.rose@canada.ca>; Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>; Cherry, Elana (HC/SC) <elana.cherry@canada.ca>; Faraci, Maria (HC/SC) <maria.faraci@canada.ca>; HC.F ORA_COVID / BAR_COVID F.SC <[hc.ora_covid-
bar_covid.sc@canada.ca](mailto:hc.ora_covid-bar_covid.sc@canada.ca)>; Ali, Osman (HC/SC) <osman.ali@canada.ca>; Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>; Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>

Subject: RE: BRDD action required: Pfizer BioNtech vaccine Memo to BRDD Control number: 251813 and 253419

Fine with me too.

De : Coleman, Gina (HC/SC) <gina.coleman@canada.ca>

Envoyé : 2021-07-13 16:43

À : Raymond, Joel (HC/SC) <joel.raymond@canada.ca>; BRDD.Risk / risque.DMBR (HC/SC) <[hc.brdd.risk-
risque.dnbr.sc@canada.ca](mailto:hc.brdd.risk-risque.dnbr.sc@canada.ca)>; Salem, Myriam (HC/SC) <myriam.salem@canada.ca>

Cc : Rose, Jhona (HC/SC) <jhona.rose@canada.ca>; Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>; Bouthillier, Leo (HC/SC) <leo.bouthillier@canada.ca>; Cherry, Elana (HC/SC) <elana.cherry@canada.ca>; Faraci, Maria (HC/SC) <maria.faraci@canada.ca>; HC.F ORA_COVID / BAR_COVID F.SC <hc.ora_covid-bar_covid.sc@canada.ca>; Ali, Osman (HC/SC) <osman.ali@canada.ca>; Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>; Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>

Objet : RE: BRDD action required: Pfizer BioNtech vaccine Memo to BRDD Control number: 251813 and 253419

It's OK with me.

Thanks,

Gina

From: Raymond, Joel (HC/SC) <joel.raymond@canada.ca>

Sent: 2021-07-13 4:35 PM

To: Coleman, Gina (HC/SC) <gina.coleman@canada.ca>; BRDD.Risk / risque.DMBR (HC/SC) <[hc.brdd.risk-
risque.dnbr.sc@canada.ca](mailto:hc.brdd.risk-risque.dnbr.sc@canada.ca)>; Salem, Myriam (HC/SC) <myriam.salem@canada.ca>

Cc: Rose, Jhona (HC/SC) <jhona.rose@canada.ca>; Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>; Bouthillier, Leo (HC/SC) <leo.bouthillier@canada.ca>; Cherry, Elana (HC/SC) <elana.cherry@canada.ca>; Faraci, Maria (HC/SC) <maria.faraci@canada.ca>; HC.F ORA_COVID / BAR_COVID F.SC <hc.ora_covid-bar_covid.sc@canada.ca>; Ali, Osman (HC/SC) <osman.ali@canada.ca>; Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>; Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>

Subject: RE: BRDD action required: Pfizer BioNtech vaccine Memo to BRDD Control number: 251813 and 253419

Hi Gina, Léo, are you OK if we send this first thing tomorrow morning?
 ORIRM would need just a tadbit more time to carefully finalise it for approvals.
 Kindest regards / Sincères salutations
 Joël

From: Raymond, Joel (HC/SC)

Sent: 2021-07-13 4:02 PM

To: Coleman, Gina (HC/SC) <gina.coleman@canada.ca>; BRDD.Risk / risque.DMBR (HC/SC) <hc.brdd.risk-risque.dnbr.sc@canada.ca>; Salem, Myriam (HC/SC) <myriam.salem@canada.ca>

Cc: Rose, Jhona (HC/SC) <jhona.rose@canada.ca>; Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>; Bouthillier, Leo (HC/SC) <leo.bouthillier@canada.ca>; Cherry, Elana (HC/SC) <elana.cherry@canada.ca>; Faraci, Maria (HC/SC) <maria.faraci@canada.ca>; HC.F ORA_COVID / BAR_COVID F.SC <hc.ora_covid-bar_covid.sc@canada.ca>; Ali, Osman (HC/SC) <osman.ali@canada.ca>; Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>; Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>

Subject: RE: BRDD action required: Pfizer BioNtech vaccine Memo to BRDD Control number: 251813 and 253419

Thanks Gina,

To confirm, AL being drafted and will be circulated shortly for approvals

Joël

From: Coleman, Gina (HC/SC) <gina.coleman@canada.ca>

Sent: 2021-07-13 2:38 PM

To: BRDD.Risk / risque.DMBR (HC/SC) <hc.brdd.risk-risque.dnbr.sc@canada.ca>; Salem, Myriam (HC/SC) <myriam.salem@canada.ca>

Cc: Rose, Jhona (HC/SC) <jhona.rose@canada.ca>; Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>; Bouthillier, Leo (HC/SC) <leo.bouthillier@canada.ca>; Cherry, Elana (HC/SC) <elana.cherry@canada.ca>; Faraci, Maria (HC/SC) <maria.faraci@canada.ca>; HC.F ORA_COVID / BAR_COVID F.SC <hc.ora_covid-bar_covid.sc@canada.ca>; Raymond, Joel (HC/SC) <joel.raymond@canada.ca>; Ali, Osman (HC/SC) <osman.ali@canada.ca>; Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>; Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>

Subject: RE: BRDD action required: Pfizer BioNtech vaccine Memo to BRDD Control number: 251813 and 253419

Thank you Winnie and all who commented.

I approve the latest version. Please go ahead with the advisement letter.

Gina

From: BRDD.Risk / risque.DMBR (HC/SC) <hc.brdd.risk-risque.dnbr.sc@canada.ca>

Sent: 2021-07-13 2:21 PM

To: Salem, Myriam (HC/SC) <myriam.salem@canada.ca>; Coleman, Gina (HC/SC) <gina.coleman@canada.ca>

Cc: Rose, Jhona (HC/SC) <jhona.rose@canada.ca>; Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>; Bouthillier, Leo (HC/SC) <leo.bouthillier@canada.ca>; Cherry, Elana (HC/SC) <elana.cherry@canada.ca>; Faraci, Maria (HC/SC) <maria.faraci@canada.ca>; HC.F ORA_COVID / BAR_COVID F.SC <hc.ora_covid-bar_covid.sc@canada.ca>; Raymond, Joel (HC/SC) <joel.raymond@canada.ca>; Ali, Osman (HC/SC) <osman.ali@canada.ca>; Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>; Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>

Subject: RE: BRDD action required: Pfizer BioNtech vaccine Memo to BRDD Control number: 251813 and 253419

Good afternoon All,

BRDD Risk will be issuing an **advisement letter** to request this set of PM update from Pfizer. We've confirmed with ORA-Covid that there is no clinical IO-amendment in house under which to request these updates via clarifax for swift turn-around.

Gina – Awaiting your agreement with the latest changes proposed by Myriam. Once approved, BRDD Risk will prepare advisement letter and circulate for CERB manager & director approval later this afternoon. We will aim for issuance by COB today, requesting response in 1-week's time.

Thanks,

Winnie

From: Salem, Myriam (HC/SC) <myriam.salem@canada.ca>

Sent: 2021-07-13 12:19 PM

To: Coleman, Gina (HC/SC) <gina.coleman@canada.ca>; Rose, Jhona (HC/SC) <jhona.rose@canada.ca>; Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>; Bouthillier, Leo (HC/SC) <leo.bouthillier@canada.ca>; Cherry, Elana (HC/SC) <elana.cherry@canada.ca>; Faraci, Maria (HC/SC) <maria.faraci@canada.ca>; HC.F ORA_COVID / BAR_COVID F.SC <hc.ora_covid-bar_covid.sc@canada.ca>; Raymond, Joel (HC/SC) <joel.raymond@canada.ca>; Ali, Osman (HC/SC) <osman.ali@canada.ca>

Cc: Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>; Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>

Subject: RE: BRDD action required: Pfizer BioNtech vaccine Memo to BRDD Control number: 251813 and 253419

Hi Gina,

We are proposing to include it in the PMI following the Uncommon paragraph. Please see revised changes in red below.

Please let us if you agree with the changes, we are open for suggestions.

Thanks,

Myriam

From: Coleman, Gina (HC/SC) <gina.coleman@canada.ca>

Sent: 2021-07-13 11:28 AM

To: Rose, Jhona (HC/SC) <jhona.rose@canada.ca>; Salem, Myriam (HC/SC) <myriam.salem@canada.ca>; Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>; Bouthillier, Leo (HC/SC) <leo.bouthillier@canada.ca>; Cherry, Elana (HC/SC) <elana.cherry@canada.ca>; Faraci, Maria (HC/SC) <maria.faraci@canada.ca>; HC.F ORA_COVID / BAR_COVID F.SC <hc.ora_covid-bar_covid.sc@canada.ca>; Raymond, Joel (HC/SC) <joel.raymond@canada.ca>; Ali, Osman (HC/SC) <osman.ali@canada.ca>

Cc: Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>; Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>

Subject: RE: BRDD action required: Pfizer BioNtech vaccine Memo to BRDD Control number: 251813 and 253419

Item 3: I think it's to reflect the changes in the PI.

From: Rose, Jhona (HC/SC) <jhona.rose@canada.ca>

Sent: 2021-07-13 11:24 AM

To: Salem, Myriam (HC/SC) <myriam.salem@canada.ca>; Coleman, Gina (HC/SC) <gina.coleman@canada.ca>; Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>; Bouthillier, Leo

(HC/SC) <leo.bouthillier@canada.ca>; Cherry, Elana (HC/SC) <elana.cherry@canada.ca>; Faraci, Maria (HC/SC) <maria.faraci@canada.ca>; HC.F ORA_COVID / BAR_COVID F.SC <hc.ora_covid-bar_covid.sc@canada.ca>; Raymond, Joel (HC/SC) <joel.raymond@canada.ca>; Ali, Osman (HC/SC) <osman.ali@canada.ca>

Cc: Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>; Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>

Subject: RE: BRDD action required: Pfizer BioNtech vaccine Memo to BRDD Control number: 251813 and 253419

Hello everyone,

Agree with the timeline. Added a few texts below (highlighted)

Also, sorry just one question about item 3. Just wondering if this is needed.

Thank you.

Jhona

From: Salem, Myriam (HC/SC) <myriam.salem@canada.ca>

Sent: 2021-07-13 11:12 AM

To: Coleman, Gina (HC/SC) <gina.coleman@canada.ca>; Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>; Bouthillier, Leo (HC/SC) <leo.bouthillier@canada.ca>; Cherry, Elana (HC/SC) <elana.cherry@canada.ca>; Faraci, Maria (HC/SC) <maria.faraci@canada.ca>; HC.F ORA_COVID / BAR_COVID F.SC <hc.ora_covid-bar_covid.sc@canada.ca>; Raymond, Joel (HC/SC) <joel.raymond@canada.ca>; Ali, Osman (HC/SC) <osman.ali@canada.ca>

Cc: Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>; Rose, Jhona (HC/SC) <jhona.rose@canada.ca>; Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>

Subject: RE: BRDD action required: Pfizer BioNtech vaccine Memo to BRDD Control number: 251813 and 253419

Hi Gina,

RSI is the Reference Safety Information; however, I have changed it below to CDS (Core Data Sheet) in red.

Thank you,

Myriam

From: Coleman, Gina (HC/SC) <gina.coleman@canada.ca>

Sent: 2021-07-13 11:07 AM

To: Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>; Bouthillier, Leo (HC/SC) <leo.bouthillier@canada.ca>; Cherry, Elana (HC/SC) <elana.cherry@canada.ca>; Faraci, Maria (HC/SC) <maria.faraci@canada.ca>; HC.F ORA_COVID / BAR_COVID F.SC <hc.ora_covid-bar_covid.sc@canada.ca>; Raymond, Joel (HC/SC) <joel.raymond@canada.ca>; Ali, Osman (HC/SC) <osman.ali@canada.ca>

Cc: Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>; Rose, Jhona (HC/SC) <jhona.rose@canada.ca>; Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>; Salem, Myriam (HC/SC) <myriam.salem@canada.ca>

Subject: RE: BRDD action required: Pfizer BioNtech vaccine Memo to BRDD Control number: 251813 and 253419

Hi Saj,

I don't think we need a meeting for this, the MHPD memo is very clear.

I suggest the following wording for the clarifax, however comments are welcome. I'm afraid I don't know what RSI means (in the 4th request).

I would give them one week to submit the Post-authorization change.

1. Please add acute facial paralysis Under section 8.2 Clinical Trial Adverse Reactions/Unsolicited Adverse Events/Serious Adverse Events

Through the clinical trial safety follow-up period to 14 November 2020, acute peripheral facial paralysis (or palsy) was reported by four participants in the COVID-19 mRNA Vaccine group. Onset was Day 37 after Dose 1 (participant did not receive Dose 2) and Days 3, 9, and 48 after Dose 2. No cases of acute peripheral facial paralysis (or palsy) were reported in the placebo group.

As frequency has not been assessed in Canada, the addition of these events as Unknown frequency is recommended:

2. The addition of facial paralysis/Bell's Palsy under section 8.3 Post-Market Adverse Reactions Nervous System Disorders: facial paralysis/Bell's Palsy

3. The addition of an Unknown frequency paragraph the following sentence in the Patient Medication Information in the paragraph below Uncommon under:

What are possible side effects from using Pfizer-BioNTech COVID-19 Vaccine? Like all vaccines, Pfizer-BioNTech COVID-19 Vaccine can cause side effects.

~~Side effects may occur at the following frequencies:~~

~~Unknown:~~

~~Facial paralysis/Bell's Palsy~~

Non-severe allergic reactions (such as rash, itching, hives or swelling of the face) and , severe allergic reactions, and Facial Paralysis/ Bell's Palsy have been reported.

4. We also request that the MAH update the Canadian Product Monograph to align with the Company Data Sheet (CDS) including but not limited to the following events Asthenia, Lethargy, Decreased appetite, Hyperhidrosis, Night sweats, Paresthesia, tachycardia and hypoesthesia.

Thanks,

Gina

From: Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>

Sent: 2021-07-13 10:49 AM

To: Bouthillier, Leo (HC/SC) <leo.bouthillier@canada.ca>; Cherry, Elana (HC/SC) <elana.cherry@canada.ca>; Faraci, Maria (HC/SC) <maria.faraci@canada.ca>; Coleman, Gina (HC/SC) <gina.coleman@canada.ca>; HC.F ORA_COVID / BAR_COVID F.SC <hc.ora_covid-bar_covid.sc@canada.ca>; Raymond, Joel (HC/SC) <joel.raymond@canada.ca>; Ali, Osman (HC/SC) <osman.ali@canada.ca>

Cc: Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>; Rose, Jhona (HC/SC) <jhona.rose@canada.ca>; Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>; Salem, Myriam (HC/SC) <myriam.salem@canada.ca>

Subject: RE: BRDD action required: Pfizer BioNtech vaccine Memo to BRDD Control number: 251813 and 253419

Looping BRDD risk team in as well. Saj

From: Alhaddad, Saj (HC/SC)

Sent: 2021-07-13 10:47 AM

To: Bouthillier, Leo (HC/SC) <leo.bouthillier@canada.ca>; Cherry, Elana (HC/SC) <elana.cherry@canada.ca>; Faraci, Maria (HC/SC) <maria.faraci@canada.ca>; Coleman, Gina (HC/SC)

<gina.coleman@canada.ca>; HC.F ORA_COVID / BAR_COVID F.SC <hc.ora_covid-bar_covid.sc@canada.ca>

Cc: Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>; Rose, Jhona (HC/SC) <jhona.rose@canada.ca>; Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>; Salem, Myriam (HC/SC) <myriam.salem@canada.ca>

Subject: BRDD action required: Pfizer BioNtech vaccine Memo to BRDD Control number: 251813 and 253419

Good morning BRDD team,

The MHPD created a memo based on the review of MSR#5 and MSR#6 on facial paralysis for the PFIZER-BIONTEH COVID-19 Vaccine: [HC6-024-e243022 \(1.0\) Reg Info - Post Market Tracker](#)

Please find actions in the memo for BRDD's immediate action. Should you require a meeting to discuss this, please let us know.

Regards,

Saj Alhaddad

A/ Senior Regulatory Project Manager - Gestionnaire principal de projets réglementaires par intérim
Bureau of Biologics, Radiopharmaceuticals and Self-Care Products | Bureau des produits

biologiques, radiopharmaceutiques et de soins autoadministrés

Marketed Health Products Directorate - (MHPD) | Direction des produits de santé commercialisés - (DPSC)

Saj.alhaddad@canada.ca

Tel : (613) 240-9514



Pfizer Canada

Affaires réglementaires / Regulatory Affairs

17300, autoroute Transcanadienne, Kirkland (Québec) H9J 2M5

17300 Trans-Canada Highway, Kirkland, QC H9J 2M5

24 May 2021

CONFIDENTIAL

Office of Regulatory Affairs
Biologic and Radiopharmaceutical Drugs Directorate
Health Canada Building #6
100 Eglantine Driveway, Address Locator: 0700A
Ottawa, Ontario K1A 0K9

Attention: Samar Eassa, B.Pharm, Senior Regulatory Affairs Officer
Office of Regulatory Affairs, Center for Regulatory Excellence, Statistics and Trials,
Biologics and Radiopharmaceutical Drugs Directorate

Subject: Pfizer-BioNTech COVID-19 Vaccine
COVID-19 Interim Order Authorization - Amendment (Expansion of Indication for
Use in Individuals 12-15 Years of Age)
Fulfilling Terms & Conditions-Risk Management Plan no.1 dated 5 May 2021

Reference: Dossier ID HC6-024-e243022; Control No. 251730
Sequence 0127 (Related Sequence 0101 and 0111)

Dear Ms. Eassa:

Reference is made to the COVID-19 Interim Order Authorization Amendment Control no. 251730 and the related Risk Management Plan (RMP) Terms & Conditions issued on 5 May 2021 for Pfizer-BioNTech COVID-19 Vaccine. We are submitting the Canadian Specific Addendum to the RMP for Pfizer-BioNTech COVID-19 Vaccine along with the recent EU RMP in order to fulfil the Terms and Conditions-RMP Condition no.1.

The information supplied herewith is considered to be confidential and covered under section 20(1) of the *Access to Information Act*. Notice of any request for access to this information, or any part thereof, is to be given in writing to:

Pfizer Canada ULC
17300 Trans-Canada Highway, Kirkland, Quebec H9J 2M5
Attention: Director, Regulatory Affairs

For all technical e-CTD queries, please submit your request via email to eSubmissions-CA@pfizer.com or communicate via fax to (514) 426-6824.

We trust that you will find this information to your satisfaction. Should you require additional information, please do not hesitate to contact me at [REDACTED] or [REDACTED] at [REDACTED]. Alternatively, you may reach us by fax at (514) 426-6824.

Sincerely,

[REDACTED]

[REDACTED] for)

[REDACTED]
Regulatory Affairs
Pfizer Canada ULC

pfizer.ca

Deng, Anvella (HC/SC)

From: Haddad, Saj (HC/SC)
Sent: 2023-12-12 9:06 AM
To: Deng, Anvella (HC/SC)
Subject: FW: BRDD action required: Pfizer BioNtech vaccine Memo to BRDD Control number: 251813 and 253419

For upload.

From: Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>
Sent: Tuesday, July 13, 2021 10:49 AM
To: Bouthillier, Leo (HC/SC) <leo.bouthillier@canada.ca>; Cherry, Elana (HC/SC) <elana.cherry@canada.ca>; Faraci, Maria (HC/SC) <maria.faraci@canada.ca>; Coleman, Gina (HC/SC) <gina.coleman@canada.ca>; HC.F ORA_COVID / BAR_COVID F.SC <hc.ora_covid-bar_covid.sc@canada.ca>; Raymond, Joel (HC/SC) <joel.raymond@canada.ca>; Ali, Osman (HC/SC) <osman.ali@canada.ca>
Cc: Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>; Rose, Jhona (HC/SC) <jhona.rose@canada.ca>; Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>; Salem, Myriam (HC/SC) <myriam.salem@canada.ca>
Subject: RE: BRDD action required: Pfizer BioNtech vaccine Memo to BRDD Control number: 251813 and 253419

Looping BRDD risk team in as well. Saj

From: Alhaddad, Saj (HC/SC)
Sent: 2021-07-13 10:47 AM
To: Bouthillier, Leo (HC/SC) <leo.bouthillier@canada.ca>; Cherry, Elana (HC/SC) <elana.cherry@canada.ca>; Faraci, Maria (HC/SC) <maria.faraci@canada.ca>; Coleman, Gina (HC/SC) <gina.coleman@canada.ca>; HC.F ORA_COVID / BAR_COVID F.SC <hc.ora_covid-bar_covid.sc@canada.ca>
Cc: Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>; Rose, Jhona (HC/SC) <jhona.rose@canada.ca>; Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>; Salem, Myriam (HC/SC) <myriam.salem@canada.ca>
Subject: BRDD action required: Pfizer BioNtech vaccine Memo to BRDD Control number: 251813 and 253419

Good morning BRDD team,

The MHPD created a memo based on the review of MSR#5 and MSR#6 on facial paralysis for the PFIZER-BIONTEH COVID-19 Vaccine: [HC6-024-e243022 \(1.0\) Reg Info - Post Market Tracker](#)

Please find actions in the memo for BRDD's immediate action. Should you require a meeting to discuss this, please let us know.

Regards,

Saj Alhaddad

A/ Senior Regulatory Project Manager - Gestionnaire principal de projets réglementaires par intérim
 Bureau of Biologics, Radiopharmaceuticals and Self-Care Products | Bureau des produits biologiques, radiopharmaceutiques et de soins autoadministrés
 Marketed Health Products Directorate - (MHPD) | Direction des produits de santé commercialisés - (DPSC)
Saj.alhaddad@canada.ca
 Tel : (613) 240-9514

Deng, Anvella (HC/SC)

From: Haddad, Saj (HC/SC)
Sent: 2023-12-12 9:05 AM
To: Deng, Anvella (HC/SC)
Subject: FW: BRDD action required: Pfizer BioNtech vaccine Memo to BRDD Control number: 251813 and 253419

For upload.

From: Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>
Sent: Tuesday, July 13, 2021 10:47 AM
To: Bouthillier, Leo (HC/SC) <leo.bouthillier@canada.ca>; Cherry, Elana (HC/SC) <elana.cherry@canada.ca>; Faraci, Maria (HC/SC) <maria.faraci@canada.ca>; Coleman, Gina (HC/SC) <gina.coleman@canada.ca>; HC.F ORA_COVID / BAR_COVID F.SC <hc.ora_covid-bar_covid.sc@canada.ca>
Cc: Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>; Rose, Jhona (HC/SC) <jhona.rose@canada.ca>; Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>; Salem, Myriam (HC/SC) <myriam.salem@canada.ca>
Subject: BRDD action required: Pfizer BioNtech vaccine Memo to BRDD Control number: 251813 and 253419

Good morning BRDD team,

The MHPD created a memo based on the review of MSR#5 and MSR#6 on facial paralysis for the PFIZER-BIONTEH COVID-19 Vaccine: [HC6-024-e243022 \(1.0\) Reg Info - Post Market Tracker](#)

Please find actions in the memo for BRDD's immediate action. Should you require a meeting to discuss this, please let us know.

Regards,

Saj Alhaddad

A/ Senior Regulatory Project Manager - Gestionnaire principal de projets réglementaires par intérim
 Bureau of Biologics, Radiopharmaceuticals and Self-Care Products | Bureau des produits biologiques, radiopharmaceutiques et de soins autoadministrés
 Marketed Health Products Directorate - (MHPD) | Direction des produits de santé commercialisés - (DPSC)
Saj.alhaddad@canada.ca
 Tel : (613) 240-9514

From: Haddad, Saj (HC/SC)
Sent: 2023-12-12 9:04 AM
To: Deng, Anvella (HC/SC)
Subject: FW: Pfizer-BioNTech COVID-19 Vaccine Monthly Summary Safety Report letter control# 253419
Attachments: 253419 Letter to MAH.pdf

For upload.

From: Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>
Sent: Monday, July 12, 2021 9:02 PM
To: 'eSubmissions-CA@pfizer.com' <eSubmissions-CA@pfizer.com>
Cc: Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>; Rose, Jhona (HC/SC) <jhona.rose@canada.ca>
Subject: Pfizer-BioNTech COVID-19 Vaccine Monthly Summary Safety Report letter control# 253419

Dear [REDACTED]

As part of Health Canada's efforts to minimize health risk factors to Canadians while maximizing the safety provided by the regulatory system for health products, the Marketed Health Products Directorate (MHPD) has completed a comprehensive review of the Summary Monthly Safety Report (SMSR) covering the period from April 30, 2021 to May 31, 2021 for **the Pfizer-BioNTech COVID-19 Vaccine (tozinameran) control number 253419**. Please find below actions for Pfizer Canada ULC and BioNTech Manufacturing GmbH stemming from this review.

Please use the assigned control number for your next Monthly Safety report, and submit the attached letter in module 1.0.3 in your sequence.

Please confirm receipt of this e-mail and the attached letter,

Thank you,

Saj Alhaddad

A/ Senior Regulatory Project Manager - Gestionnaire principal de projets réglementaires par intérim
Bureau of Biologics, Radiopharmaceuticals and Self-Care Products | Bureau des produits biologiques, radiopharmaceutiques et de soins autoadministrés
Marketed Health Products Directorate - (MHPD) | Direction des produits de santé commercialisés - (DPSC)

Saj.alhaddad@canada.ca

Tel : (613) 240-9514



Marketed Health Products Directorate
Address Locator # 1906A
OTTAWA, Ontario
K1A 0K9

Date: July 12, 2021

Control #: 253419

[REDACTED] Regulatory Affairs
Pfizer Canada ULC
17300 Trans-Canada Highway
KIRKLAND, Quebec
H9J 2M5

Email: ESUBMISSIONS-CA@PFIZER.COM

Dear Ms. [REDACTED]

Re: Pfizer-BioNTech COVID-19 Vaccine (tozinameran)

As part of Health Canada's efforts to minimize health risk factors to Canadians while maximizing the safety provided by the regulatory system for health products, the Marketed Health Products Directorate (MHPD) has completed a comprehensive review of the Summary Monthly Safety Report (SMSR) covering the period from April 30, 2021 to May 31, 2021 for **the Pfizer-BioNTech COVID-19 Vaccine (tozinameran) control number 253419**. Please find below actions for Pfizer Canada ULC and BioNTech Manufacturing GmbH stemming from this review.

In accordance with the Risk Management Plan Terms and Conditions, imposed under the *Interim Order Respecting the Importation, Sale and Advertising of Drugs for Use in Relation to Covid-19*, Pfizer Canada ULC is required to submit monthly safety reports for the period of the Interim Order authorization. As such, you are requested to submit the monthly safety report for the period of **June 01, 2021 to June 30, 2021** including cumulative number of reports (serious and non-serious) and adverse events that occurred in Canada and globally for the **Pfizer-BioNTech COVID-19 Vaccine (tozinameran)** known to **Pfizer Canada ULC and BioNTech Manufacturing GmbH**.

Actions for Pfizer Canada ULC and BioNTech Manufacturing GmbH stemming from the SMSR #6 review are to:

1. **Facial paralysis /Bell's Palsy:** From Pfizer's response to the letter issued on June 7, 2021, the following were noted: *With regards to the question on Facial paralysis /Bell's Palsy in association with the Pfizer-BioNTech COVID-19 Vaccine, the analysis on overall data in subjects reporting facial paralysis/Bell's palsy after BNT162b2 vaccination, including clinical study data, postauthorization reports and observed to expected analyses, provides inconclusive evidence of a causal association with BNT162b2. Evaluations will continue and*



Bell's palsy is an endpoint in Pfizer's observational surveillance studies. Updates to labeling language will be proposed if warranted upon future assessment.

Health Canada would like to reiterate that based on the imbalance observed in the clinical trials, increase in frequency of reporting from the post-market data, and safety information captured in the EMA SmPC, EUA USPI (including Bell's Palsy) and MHRA, Health Canada's position remains the same and the need for further risk mitigation will be discussed with our pre-market colleagues.

2. In addition, the Pfizer's response to the letter issued on June 7, 2021 noted the following: *All planned safety-related updates to the Core Data Sheet are captured in the Summary Monthly Safety Report (SMSR). As mentioned at the pre-New Drug Submission (NDS) meeting held with Health Canada (HC) on 3 June 2021, Pfizer plans on requesting a meeting with HC in the coming weeks to discuss upcoming revisions to the Product Monograph which will be filed under the second roll of the NDS CV as well as in parallel via an Interim Order Amendment.*

It is our understanding from the conversation on June 21, 2021 that Pfizer will soon submit a post-market label update to align labelling with the Core Data Sheet.

3. Include in the SMSR to be submitted by August 15, 2021:
 - a. A cumulative review of the following safety topics given the seriousness of the cases including fatalities
 - b. Cardiovascular events namely, myocardial infarction, cardiac failure
 - c. Seizure (using the search criteria identified previously by HC)
 - d. Arterial Thromboembolic events (Stroke)
 - e. Venous Thromboembolic events (deep venous thrombosis [DVT] and pulmonary embolism [PE]), using: the Standard MedDRA Query (SMQ) narrow "Embolic and thrombotic events, venous"

Data should be stratified by sex, age, gender, dose 1 or dose 2 and assessed for causality using Brighton Collaboration Definition Criteria. The observed and expected analyses should be included. An analysis of Canadian cases including an assessment on causality is also requested. Once the assessment is completed the MAH should also provide a discussion on the need to update the product monograph and/or update the risk management plan.

4. Discuss the need to implement a registry with reference in the CPM for pregnant women given that cases with serious outcomes are being reported to the Canadian databases. This approach will be consistent with the other COVID vaccines currently available in Canada. .



As a general reminder, a Notification of Foreign Action should be submitted to the MHPD in accordance with subsection C.01.050 of the *Food and Drug Regulations*, when appropriate. When safety updates are implemented in other jurisdictions Health Canada would like consideration to be given by the MAH with regards to implementation of these updates in the Canadian Product Monograph. In Addition, please provide the safety reports prepared for other regulatory agencies with the MSSR submissions.

A control number has been assigned for your submission of a monthly safety report in response to this letter. The control number is **254572**. Please provide the monthly safety report before or on **July15, 2021** and include this control number in the cover letter of your response, along with a copy of this letter.

Sponsors must now submit their regulatory transactions using the Regulatory Enrolment Process (REP). By using this process, transactions in both eCTD and non-eCTD formats can be securely submitted via the Common Electronic Submissions Gateway (CESG).

Questions concerning this request should be directed to Saj Alhaddad, Acting Senior Regulatory Project Manager, BBRS, MHPD, by email at hc.mbbnhpb.rpmgpr.bpbbbsnc.sc@canada.ca.

Thank you in advance for your cooperation.

Melissa Hunt
Director
Marketed Health Products Directorate

This document has been signed electronically using the Health Canada docuBridge system. /
Ce document a été signé électroniquement à l'aide du système docuBridge de Santé Canada.

Deng, Anvella (HC/SC)

From: Haddad, Saj (HC/SC)
Sent: 2023-12-12 9:05 AM
To: Deng, Anvella (HC/SC)
Subject: FW: For Director Review/Signature Pfizer BioNtech vaccine MSR6 and letter to MAH (DSTS#253419)

For upload.

From: Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>
Sent: Tuesday, July 13, 2021 8:40 AM
To: Rose, Jhona (HC/SC) <jhona.rose@canada.ca>; Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>; Salem, Myriam (HC/SC) <myriam.salem@canada.ca>
Cc: Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>
Subject: RE: For Director Review/Signature Pfizer BioNtech vaccine MSR6 and letter to MAH (DSTS#253419)

I agree with the classification and I also agree with Jhona, Myriam, this was a review of facial paralysis of Pfizer only correct? If so we should remove “moderna” from the subject line as Jhona suggested.
 Saj

From: Rose, Jhona (HC/SC) <jhona.rose@canada.ca>
Sent: 2021-07-13 8:27 AM
To: Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>; Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>; Salem, Myriam (HC/SC) <myriam.salem@canada.ca>
Cc: Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>
Subject: RE: For Director Review/Signature Pfizer BioNtech vaccine MSR6 and letter to MAH (DSTS#253419)

Good morning,
 I just quickly check the memo. The subject line is for Pfizer and Moderna but the summary data only covered Pfizer. Moderna is not mentioned anywhere else in the document.
 Thank you.
 Jhona

From: Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>
Sent: 2021-07-13 7:54 AM
To: Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>; Salem, Myriam (HC/SC) <myriam.salem@canada.ca>
Cc: Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>; Rose, Jhona (HC/SC) <jhona.rose@canada.ca>
Subject: RE: For Director Review/Signature Pfizer BioNtech vaccine MSR6 and letter to MAH (DSTS#253419)

Thank you Saj,

I added “Protected B” as security classification (I think that is what it would be). If any disagree let me know shortly (I will sign around 9).

Thanks

From: Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>
Sent: 2021-07-12 8:59 PM
To: Salem, Myriam (HC/SC) <myriam.salem@canada.ca>; Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>
Cc: Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>; Rose, Jhona (HC/SC) <jhona.rose@canada.ca>
Subject: RE: For Director Review/Signature Pfizer BioNtech vaccine MSR6 and letter to MAH (DSTS#253419)

Made some edits, added the control numbers for MSSR 5 and 6 for Pfizer and updated the metadata as well. Saj

From: Salem, Myriam (HC/SC) <myriam.salem@canada.ca>
Sent: 2021-07-12 4:25 PM
To: Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>; Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>
Cc: Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>; Rose, Jhona (HC/SC) <jhona.rose@canada.ca>
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Sent: 2021-07-12 4:18 PM
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Sent: Monday, July 12, 2021 8:59 PM
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HC6-024-e243022 (1.0) Reg Info - Post Market Tracker

HC6-024-e243022 (1.0) Reg Info - Post Market Tracker

The documents were also shared with Saj and Tonja.

Thank you,
Myriam

Deng, Anvella (HC/SC)

From: Haddad, Saj (HC/SC)
Sent: 2023-12-12 9:03 AM
To: Deng, Anvella (HC/SC)
Subject: FW: For Director Review/Signature Pfizer BioNtech vaccine MSR6 and letter to MAH (DSTS#253419)

For upload.

From: Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>
Sent: Friday, July 9, 2021 10:59 AM
To: Salem, Myriam (HC/SC) <myriam.salem@canada.ca>; Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>
Cc: Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>
Subject: RE: For Director Review/Signature Pfizer BioNtech vaccine MSR6 and letter to MAH (DSTS#253419)

I added the control number and made minor edits. Saj

From: Salem, Myriam (HC/SC) <myriam.salem@canada.ca>
Sent: 2021-07-09 10:52 AM
To: Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>; Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>
Cc: Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>
Subject: RE: For Director Review/Signature Pfizer BioNtech vaccine MSR6 and letter to MAH (DSTS#253419)

Thank you Saj,

Please find below the corrected link:
[HC6-024-e243022 \(1.0\) Reg Info - Post Market Tracker](#)

Thanks,
 Myriam

From: Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>
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To: Salem, Myriam (HC/SC) <myriam.salem@canada.ca>; Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>
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 FYI the report is from April 30 to May 31 if we wish to make that edit on the cover page of the report.
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 Regards,
 Saj

From: Salem, Myriam (HC/SC) <myriam.salem@canada.ca>
Sent: 2021-07-09 10:28 AM
To: Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>

Document Released Under the Access to Information Act
Cc: Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>; Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>

Subject: For Director Review/Signature Pfizer BioNtech vaccine MSR6 and letter to MAH (DSTS#253419)

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[HC6-024-e243022 \(1.0\) Reg Info - Post Market Tracker](#)

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Myriam

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To: Salem, Myriam (HC/SC) <myriam.salem@canada.ca>; Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>
Cc: Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>
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Subject: For Director Review/Signature Pfizer BioNtech vaccine MSR6 and letter to MAH (DSTS#253419)

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HC6-024-e243022 (1.0) Reg Info - Post Market Tracker
HC6-024-e243022 (1.0) Reg Info - Post Market Tracker

The documents were also shared with Saj and Tonja.

Thank you,
 Myriam

Deng, Anvella (HC/SC)

From: Haddad, Saj (HC/SC)
Sent: 2023-12-12 9:02 AM
To: Deng, Anvella (HC/SC)
Subject: FW: Project assigned - Pfizer-BioNTech COVID-19 vaccine, Monthly Summary Safety Report control# 253419

For upload.

From: Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>
Sent: Wednesday, June 16, 2021 4:03 PM
To: Salem, Myriam (HC/SC) <myriam.salem@canada.ca>
Cc: Rose, Jhona (HC/SC) <jhona.rose@canada.ca>; Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>
Subject: Project assigned - Pfizer-BioNTech COVID-19 vaccine, Monthly Summary Safety Report control# 253419

Hi Myriam,

You have been assigned to the Pfizer-BioNTech COVID-19 vaccine Monthly Summary Safety Report #6 review (Control # 253419). Please use SAP code: 253419

Review drafts and documents should be saved in the following folder:

Y:\HC\HPFB\MHPD\MBBNHPB\X_REFERENCE\BBRS CRT\Submissions\Pfizer-BioNTech Covid-19 Vaccine [Pfizer Canada ULC]\243419 Monthly Safety Report # 6

The DocuBridge link of the Monthly Summary Safety Report #6: HC6-024-e243022 (0133) Biologic Dossier

Target for first draft to Jhona: July 2, 2021 a reminder e-mail will be sent on June 30, 2021

Target for director approval: July 7, 2021

Thank you,

Saj Alhaddad

A/ Senior Regulatory Project Manager - Gestionnaire principal de projets réglementaires par intérim
 Bureau of Biologics, Radiopharmaceuticals and Self-Care Products | Bureau des produits biologiques,
 radiopharmaceutiques et de soins autoadministrés
 Marketed Health Products Directorate - (MHPD) | Direction des produits de santé commercialisés - (DPSC)
Saj.alhaddad@canada.ca
 Tel : (613) 240-9514

From: [Salem, Myriam \(HC/SC\)](#)
Sent: 2021-07-12 9:04 AM
To: [Rose, Jhona \(HC/SC\)](#)
Subject: FW: For Director Review/Signature Pfizer BioNtech vaccine MSR6 and letter to MAH (DSTS#253419)
Attachments: 253419_Pfizer BioNTech SMSR 6_MEMO to BRDD_0.1.docx

Hi Jhona,

Welcome back!

There were a few iterations to the MSR last week.

I have uploaded and addressed the latest comments from Melissa +letter + sent a memo for review (Melissa had a discussion with BRDD and it was decided that all labeling changes will go through them).

Myriam

From: Salem, Myriam (HC/SC)
Sent: 2021-07-09 5:36 PM
To: Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>; Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>
Cc: Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>
Subject: RE: For Director Review/Signature Pfizer BioNtech vaccine MSR6 and letter to MAH (DSTS#253419)

Sorry for the multiple emails, I have corrected the Subject of the memo.

Thanks,

Myriam

From: Salem, Myriam (HC/SC)
Sent: 2021-07-09 5:34 PM
To: Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>; Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>
Cc: Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>
Subject: RE: For Director Review/Signature Pfizer BioNtech vaccine MSR6 and letter to MAH (DSTS#253419)

Hi Melissa,

Please find attached the corresponding memo for your review.

Thanks,

Myriam

From: Salem, Myriam (HC/SC)
Sent: 2021-07-09 4:32 PM
To: Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>; Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>
Cc: Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>
Subject: RE: For Director Review/Signature Pfizer BioNtech vaccine MSR6 and letter to MAH (DSTS#253419)

Thank you Melissa, I have updated the MSR, and addressed the comments. Will follow shortly with the memo for your review.

Merci beaucoup,
Myriam

From: Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>
Sent: 2021-07-09 3:30 PM
To: Salem, Myriam (HC/SC) <myriam.salem@canada.ca>; Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>
Cc: Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>
Subject: RE: For Director Review/Signature Pfizer BioNtech vaccine MSR6 and letter to MAH (DSTS#253419)

Hi Myriam,

I have a few additional changes and comments in the docubridge version. Also invite Tonja if anything additional.

I think we will likely wrap this up on Monday morning. As discussed we'll need a memo to BRDD for the labelling changes too.

Thank you so very much!
Melissa

From: Salem, Myriam (HC/SC) <myriam.salem@canada.ca>
Sent: 2021-07-09 10:52 AM
To: Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>; Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>
Cc: Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>
Subject: RE: For Director Review/Signature Pfizer BioNtech vaccine MSR6 and letter to MAH (DSTS#253419)

Thank you Saj,

Please find below the corrected link:

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Subject: For Director Review/Signature Pfizer BioNtech vaccine MSR6 and letter to MAH (DSTS#253419)

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[HC6-024-e243022 \(1.0\) Reg Info - Post Market Tracker](#)
[HC6-024-e243022 \(1.0\) Reg Info - Post Market Tracker](#)

The documents were also shared with Saj and Tonja.

Thank you,
Myriam

From: [Salem, Myriam \(HC/SC\)](#)
Sent: 2021-08-25 1:21 PM
To: [Chen, Stella \(HC/SC\)](#)
Subject: Letter to MAH following the MSR#6 review including requests to be included in MSR#8
Attachments: ~db5_O73cb74dc1540432c9cc6d2b7dfda03ba.docx

Hi Stella,

Fyi. Please find the letter we sent to the MAH following the review of MSR#6 including cumulative reviews to be included in MSR#8.

Thanks,
Myriam



Marketed Health Products Directorate
Address Locator # 1906A
OTTAWA, Ontario
K1A 0K9

Date: July 12, 2021

Control #: 253419

[REDACTED]
[REDACTED] Regulatory Affairs
Pfizer Canada ULC
17300 Trans-Canada Highway
KIRKLAND, Quebec
H9J 2M5

Email: ESUBMISSIONS-CA@PFIZER.COM

Dear Ms. [REDACTED]

Re: Pfizer-BioNTech COVID-19 Vaccine (tozinameran)

As part of Health Canada's efforts to minimize health risk factors to Canadians while maximizing the safety provided by the regulatory system for health products, the Marketed Health Products Directorate (MHPD) has completed a comprehensive review of the Summary Monthly Safety Report (SMSR) covering the period from April 30, 2021 to May 31, 2021 for **the Pfizer-BioNTech COVID-19 Vaccine (tozinameran) control number 253419**. Please find below actions for Pfizer Canada ULC and BioNTech Manufacturing GmbH stemming from this review.

In accordance with the Risk Management Plan Terms and Conditions, imposed under the *Interim Order Respecting the Importation, Sale and Advertising of Drugs for Use in Relation to Covid-19*, Pfizer Canada ULC is required to submit monthly safety reports for the period of the Interim Order authorization. As such, you are requested to submit the monthly safety report for the period of **June 01, 2021 to June 30, 2021** including cumulative number of reports (serious and non-serious) and adverse events that occurred in Canada and globally for the **Pfizer-BioNTech COVID-19 Vaccine (tozinameran)** known to **Pfizer Canada ULC and BioNTech Manufacturing GmbH**.

Actions for Pfizer Canada ULC and BioNTech Manufacturing GmbH stemming from the SMSR #6 review are to:

1. **Facial paralysis /Bell's Palsy:** From Pfizer's response to the letter issued on June 7, 2021, the following were noted: *With regards to the question on Facial paralysis /Bell's Palsy in association with the Pfizer-BioNTech COVID-19 Vaccine, the analysis on overall data in subjects reporting facial paralysis/Bell's palsy after BNT162b2 vaccination, including clinical study data, postauthorization reports and observed to expected analyses, provides inconclusive evidence of a causal association with BNT162b2. Evaluations will continue and*

Bell's palsy is an endpoint in Pfizer's observational surveillance studies. Updates to labeling language will be proposed if warranted upon future assessment.

Health Canada would like to reiterate that based on the imbalance observed in the clinical trials, increase in frequency of reporting from the post-market data, and safety information captured in the EMA SmPC, EUA USPI (including Bell's Palsy) and MHRA, Health Canada's position remains the same and the need for further risk mitigation will be discussed with our pre-market colleagues.

2. In addition, the Pfizer's response to the letter issued on June 7, 2021 noted the following: *All planned safety-related updates to the Core Data Sheet are captured in the Summary Monthly Safety Report (SMSR). As mentioned at the pre-New Drug Submission (NDS) meeting held with Health Canada (HC) on 3 June 2021, Pfizer plans on requesting a meeting with HC in the coming weeks to discuss upcoming revisions to the Product Monograph which will be filed under the second roll of the NDS CV as well as in parallel via an Interim Order Amendment.*

It is our understanding from the conversation on June 21, 2021 that Pfizer will soon submit a post-market label update to align labelling with the Core Data Sheet.

3. Include in the SMSR to be submitted by August 15, 2021 :
 - a. A cumulative review of the following safety topics given the seriousness of the cases including fatalities
 - b. Cardiovascular events namely, myocardial infarction, cardiac failure
 - c. Seizure (using the search criteria identified previously by HC)
 - d. Arterial Thromboembolic events (Stroke)
 - e. Venous Thromboembolic events (deep venous thrombosis [DVT] and pulmonary embolism [PE]), using: the Standard MedDRA Query (SMQ) narrow "Embotic and thrombotic events, venous"

Data should be stratified by sex, age, gender, dose 1 or dose 2 and assessed for causality using Brighton Collaboration Definition Criteria. The observed and expected analyses should be included. An analysis of Canadian cases including an assessment on causality is also requested. Once the assessment is completed the MAH should also provide a discussion on the need to update the product monograph and/or update the risk management plan.

4. Discuss the need to implement a registry with reference in the CPM for pregnant women given that cases with serious outcomes are being reported to the Canadian databases. This approach will be consistent with the other COVID vaccines currently available in Canada. .

As a general reminder, a Notification of Foreign Action should be submitted to the MHPD in accordance with subsection C.01.050 of the *Food and Drug Regulations*, when appropriate. When safety updates are implemented in other jurisdictions Health Canada would like consideration to be given by the MAH with regards to implementation of these updates in the Canadian Product Monograph. In Addition, please provide the safety reports prepared for other regulatory agencies with the MSSR submissions.

A control number has been assigned for your submission of a monthly safety report in response to this letter. The control number is **254572**. Please provide the monthly safety report before or on **July 15, 2021** and include this control number in the cover letter of your response, along with a copy of this letter.

Sponsors must now submit their regulatory transactions using the Regulatory Enrolment Process (REP). By using this process, transactions in both eCTD and non-eCTD formats can be securely submitted via the Common Electronic Submissions Gateway (CESG).

Questions concerning this request should be directed to Saj Alhaddad, Acting Senior Regulatory Project Manager, BBRS, MHPD, by email at hc.mbbnhpb.rpmgpr.bpbbbsnc.sc@canada.ca.

Thank you in advance for your cooperation.

Melissa Hunt
Director
Marketed Health Products Directorate

This document has been signed electronically using the Health Canada docuBridge system. /
Ce document a été signé électroniquement à l'aide du système docuBridge de Santé Canada.

From: Salem, Myriam (HC/SC)
Sent: 2021-06-27 1:27 AM
To: Salem, Myriam (HC/SC)
Subject: Myocarditis_AdHoc_2021-06-25_0.3.docx
Attachments: Myocarditis_AdHoc_2021-06-25_0.3.docx

Marketed Health Products Directorate
Direction des produits de santé commercialisés

AdHoc Report

**messenger ribonucleic acid (mRNA) COVID-19 Vaccines
Myocarditis/Pericarditis**

Control #

Position Title: Director / Directeur(ice)
Bureau: Choose an item.
Date: <Enter date of completion>
Signature: <i>This document has been signed electronically using the Health Canada docuBridge system.</i> / Ce document a été signé électroniquement à l'aide du système docuBridge de Santé Canada
Security – Classification – de sécurité: Protected B when completed / protégé B une fois terminé

Inclusion of confidential information (i.e., shared by another regulatory agency) into the assessment should be clearly identified (highlighted) and should be included if considered necessary.

MHPD – PROTECTED B

REVIEW REPORT

Title: Review Report: Drug name (generic name followed by trade name® in brackets) and adverse event

Date:

CONTENTS

1. Issue:	3
2. Purpose:.....	4
3. Background and Issue Analysis:.....	4
4. Considerations :	20
5. Recommendations:.....	21
6. References:.....	23

DRAFT

MHPD – PROTECTED B**REVIEW REPORT**

1. Issue:

mRNA vaccines have been authorized in Canada under a ministerial Interim Order in December 2020. There are currently two (2) mRNA vaccines authorized for use in Canada. The Pfizer-BioNTech COVID-19 Vaccine, also known as BNT and the Moderna Covid-19 Vaccine. Both vaccines are indicated for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS- CoV-2). On May 05th the Pfizer vaccine received authorization to expand the indication to adolescents 12 to 15 years of age.

The signal of myocarditis was first detected when the Israel Ministry of Health noted a cluster of myocarditis cases following the mRNA Pfizer Covid-19 vaccine in February 2021. Following the review of monthly safety update report for February 2021, no new signal was identified; however, Health Canada requested more information on cardiac issues such as Cardiac Failure, and Myocardial infarction.

In March 2021, the U.S. Food Drugs Administration (FDA), European Medicines Agency (EMA), MHRA, Japan Pharmaceuticals and Medical Devices Agency (PMDA) and Health Canada discussed myocarditis at the Pharmacovigilance Cluster teleconference. It was agreed at that time there was no safety signal and standard post-market monitoring would continue for this issue. In the Monthly Safety Update Report #3 for March 2021 submitted to Health Canada, Pfizer noted a total of 72 myocarditis case reports since marketing and indicated that the observed rate of myocarditis did not exceed the expected rate in a general population (4.40 cases per 100,000 people/year). The report did not identify myocarditis as a validated safety signal. Health Canada reached out to Pfizer as well as the Ministry of Health in Israel for more information on the myocarditis reports in that jurisdiction. Pfizer did not consider the available evidence would support a safety signal, but confirmed the company will continue to monitor this issue.

On April 19, 2021, at the request of the MHRA, the MAH re-opened the signal to determine if myocarditis or pericarditis is a risk following vaccination of Pfizer BioNtech.

On May 15, 2021, Pfizer provided a cumulative review of Myocarditis and Pericarditis in the Monthly Summary Safety Report #5 for April 2021. The database was searched for spontaneous adverse events reports for Pfizer/BNT COVID-19 vaccine up to 17 April 2021. Pfizer identified 39 cases categorized as having some degree of certainty in diagnosis of myocarditis (definite, probable and possible cases). Pfizer concluded that there is no causal association based on the observed vs expected rates of myocarditis, pericarditis, clinical trial experience and post-authorization reports and closed the signal. The MHPD did not agree with this assessment. The MHPD requested a discussion on the risk mitigation strategies to be implemented in Canada, including PM safety update and recommended this issue be monitored separately from the monthly safety reports.

MHPD – PROTECTED B

REVIEW REPORT

2. Purpose:

The goal of this adHoc report is to continue monitoring and assessing emerging information on myocarditis with the mRNA vaccines in Canada and to determine the need for implementation of risk mitigation measures.

3. Background:

Product classification and Indications in Canada

There are currently two (2) COVID-19 mRNA Vaccines authorized in Canada:

1. PFIZER-BIONTECH COVID-19 VACCINE, also referred to as BNT162, is indicated for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS- CoV-2) in individuals 12 years of age and older.
2. COVID-19 Vaccine Moderna indicated for Active immunization against coronavirus disease 2019 (COVID-19) caused by the SARS-CoV-2 virus in individuals 18 years of age and older.

Most of the evidence in this review report relates to the Pfizer-BioNtech vaccine; however, evidence related to Covid-19 vaccine Moderna is also being considered. As of June 23, 2021, the Pfizer BioNtech vaccine is the only Covid vaccine authorized for use in adolescents 12 to 17 years of age.

The independent vaccine advisory committee in Canada, NACI, gave its approval on

International indications

European Medicines Agency

In the European Union, both mRNA vaccines: Pfizer-BioNTech (referred to as *Comirnaty*¹) and Moderna (referred to as *Spikevax*²) vaccines are indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus in adult patients but similar to Canada only the Pfizer-BioNTech vaccine is authorized in individuals 12 years of age and older. Spikevax is indicated in individuals 18 years of age and older.

Differences across EU member states exist when it comes to the use of the vaccine in the children/adolescents population. According to official recommendations stemming from independent member states vaccines committees, some members have limited the use in this patient population as illustrated by the examples below:

¹ https://www.ema.europa.eu/en/documents/product-information/comirnaty-epar-product-information_en.pdf

² <https://www.ema.europa.eu/en/medicines/human/EPAR/spikevax-previously-covid-19-vaccine-moderna>

MHPD – PROTECTED B**REVIEW REPORT***The Netherlands*

On June 9, 2021, the Dutch Health Council gave a positive recommendation to begin vaccinating children aged 12 to 15³ who are vulnerable to serious symptoms of the coronavirus disease in addition to those aged 16 and 17 from high-risk groups⁴.

Germany

On June 10, 2021, the German vaccine advisory committee, the Standing Committee on vaccination (STIKO), gave limited approval for the pediatric indication given the lack of data on long-term effects. As reported by Reuters⁵, the panel said *it was not currently recommending the use of the vaccine for those aged 12-17 without pre-existing conditions, although noted doctors were allowed to give the shot if the individual accepts the risk.*

United Kingdom (UK)

On June 16, 2021, news reports⁶⁷ suggested that the Joint Committee on Vaccination and Immunisation (JCVI) will not advise the Government to press ahead with a vaccination campaign for under-18s.

Food and Drug Administration

In the United States, both the Pfizer-BioNTech and Moderna mRNA vaccines were granted an Emergency Use Authorization (EUA) to permit the emergency use of these unapproved products, Pfizer-BioNTech COVID-19 Vaccine, and for active immunization to prevent COVID-19 in individuals 18 years of age and older. Similar to Canada, the Pfizer-BioNTech vaccine was authorized for use in individuals 12 years of age and older on May 10, 2021.

Israel

In Israel, the Pfizer-BioNTech vaccine is the only vaccine authorized for use in individuals 12 years of age and older.

³ [Netherlands-will-give-covid-vaccines-medically-vulnerable-adolescents](#)

⁴ [Covid-vaccination-starts-16-18-year-olds-high-risk-groups](#)

⁵ [German-panel-gives-limited-approval-covid-19-shot-adolescents](#)

⁶ [JCVI-not-recommending-vaccinating-children](#)

⁷ [Vaccination-experts-are-not-recommending-covid-jabs-for-under-18s-says-cabinet-minister](#)

MHPD – PROTECTED B**REVIEW REPORT*****Mechanism of action***

The nucleoside-modified messenger ribonucleic acid (mRNA) in the Pfizer-BioNTech COVID-19 Vaccine is formulated in lipid nanoparticles, which enable delivery of the mRNA into the host's cells to allow expression of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike antigen⁸. The protection against COVID-19 disease may be attributed to both the neutralizing antibody and immune cellular responses to the spike antigen⁹.

The mechanism of action of the Moderna Vaccine is similar to the Pfizer BioNtech COVID-19 Vaccine. As per the Product Monograph¹⁰ the COVID-19 Vaccine Moderna encodes for the pre-fusion stabilized Spike protein of SARS-CoV-2. After intramuscular injection, cells take up the lipid nanoparticle, effectively delivering the mRNA sequence into cells for expression of the SARS-CoV-2 S antigen. The vaccine induces both neutralizing antibody and cellular immune responses to the spike (S) antigen, which may contribute to protection against COVID-19 disease.

Both vaccines require 2 injections

Biological Plausability

The mechanism of myocarditis/pericarditis following mRNA COVID vaccination is not clear. There are numerous proposed mechanisms that include

In case reports in the literature involving myocarditis following mRNA COVID-19 vaccination

Description of the Adverse Event

Myocarditis is an inflammatory disease of cardiac muscle that is caused by a variety of infectious and noninfectious conditions in adults¹¹. The incidence of myocarditis in children estimated at 1 to 2 per 100,000 children. Peaks in infancy and adolescents have been reported in the medical literature. Clinical manifestations include a broad spectrum of signs including non-specific symptoms such as respiratory distress, and exhaustion. In severe cases, myocarditis may lead to cardiogenic shock and sudden death.

⁸ Summary Basis of Decision - Pfizer-BioNTech COVID-19 Vaccine - Health Canada

⁹ Product Monograph Pfizer-BioNTech COVID-19 Vaccine dated May 19, 2021

¹⁰ Product Monograph COVID-19 Vaccine Moderna dated June 09, 2021.

¹¹ Clinical-manifestations-and-diagnosis-of-myocarditis-in-adults

MHPD – PROTECTED B**REVIEW REPORT**

Myocarditis following mRNA vaccination has yet to be fully characterized; however, the spectrum of clinical manifestations appear to be less severe with most patients responding well to treatment and recovering quickly¹².

Issue Analysis***Regulatory assessments and/or Actions in Canada and internationally including vaccines committee recommendations******Current Product Monograph (PM) Labelling and International Labelling*****Health Canada**

There is no labelling for ‘myocarditis’, “myopericarditis”, pericarditis or related myocarditis laboratory findings (elevation of troponin levels) in the current CPM (dated May 19, 2021) for the Pfizer BioNTech Covid vaccine or any other currently COVID-19 vaccine in Canada including the mRNA vaccine from Moderna.

European Medicines Agency (EMA)

In the EU, similar to Canada, there is no labelling for ‘myocarditis’ for any of the COVID-19 approved vaccines. Of note, the PRAC adopted a recommendation to initiate a signal assessment on this issue. Recommendations stemming from this review will be shared during the next PRAC meeting currently scheduled on July 24, 2021

Food and Drugs Administration

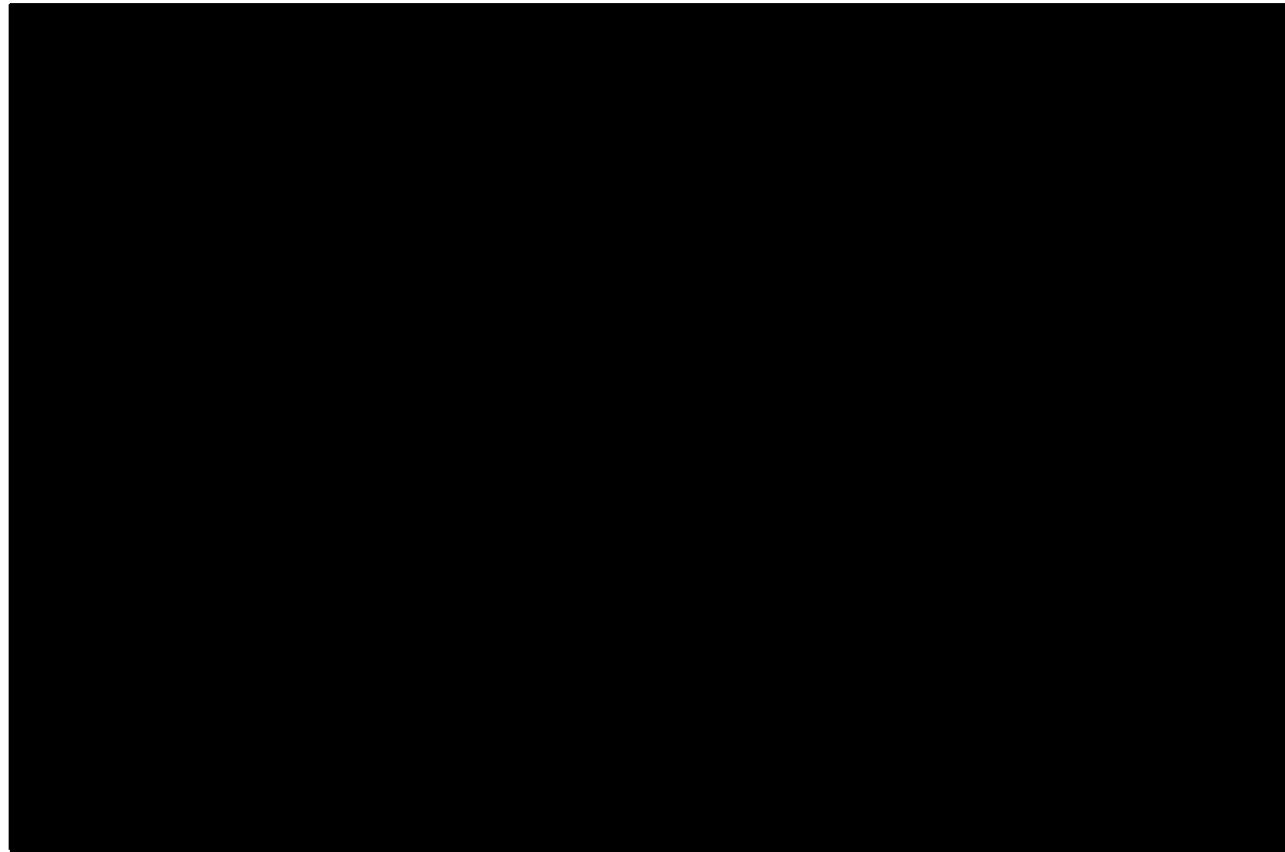
In the US, similar to Canada, there is no current labelling for ‘myocarditis’ for any of the COVID-19 approved vaccines.

Other regulatory agencies

There is no labeling for myocarditis in the Australian Therapeutic Goods Administration (TGA) label for the Pfizer Biontech vaccine, in the MedSafe New Zealand Data Sheet, the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) Drug Information sheet or the Israel information sheet.

¹² <https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/myocarditis.html>

¹³ As of June 22, 2021

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Analysis of Adverse Events in Canada and Internationally

Cases reported during the clinical development

There were no case of myocarditis occurring after the Pfizer BioNTech mRNA vaccine and COVID-19 Moderna vaccines in the trials at time of authorization^{17,18}.

As reported by Pfizer in the monthly safety report #5¹⁹ *during the blinded placebo-controlled fol)low-up period, from study C4591001 (data-lock Mar 31, 2021)there was one report of*

¹⁴ [Health Product InfoWatch – June 2021 - Canada.ca](#)

¹⁵ <https://www.gov.uk/government/publications/regulatory-approval-of-pfizer-biontech-vaccine-for-covid-19/information-for-healthcare-professionals-on-pfizerbiontech-covid-19-vaccine>

¹⁶ <https://www.gov.uk/government/publications/regulatory-approval-of-covid-19-vaccine-moderna/information-for-healthcare-professionals-on-covid-19-vaccine-moderna>

¹⁷ Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, Diemert D, Spector SA, Rouphael N, Creech CB, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. N Engl J Med. 2021;384:403-416.

¹⁸ 2. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, Perez JL, Pérez Marc G, Moreira ED, Zerbini C, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med. 2020 Dec 31;383:2603-2615

¹⁹ [HC6-024-e243022 \(251813 - For Period of 2021-04-01 to 2021-04-29\) - Summary Monthly Safety Report \(SMSR\) 5 01-Apr-2021 through 29-Apr-2021\)](#) :

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myocarditis in the placebo group, and one report of pericarditis in the BNT162b2 group (a 66 year old white male who had pericarditis 29 days after dose 2 of vaccine which was ongoing at the time of the data cut-off. The case was assessed as not related to study intervention by the investigator.

Cases reported in the Pfizer BioNTech Monthly Safety Reports

In the Monthly Safety report #5 (DSTS# 251813, Review report: HC6-024-e243022 (1.0) Reg Info - Post Market Tracker) Pfizer assessed the cases of myocarditis (up to April, 29, 2021).

Pfizer retrieved 278 reports of myocarditis and/or pericarditis and eliminated the ones that:

- did not contain enough clinical detail;
- described pericardial effusion without pericarditis or myocarditis;
- described pericardial effusion attributed to other diseases
- did not contain information describing pericarditis or myocarditis
- had an alternative explanations for pericarditis or myocarditis (including current COVID-19, history of autoimmune condition, renal failure, histories of tuberculosis.

The MAH analyzed the remaining 216 cases. From the analysis of the 216 cases, a pattern emerges from the time to vaccination to the emergence of myocarditis and/or pericarditis. The majority of cases were reported from the same day of vaccination up to 7 days following vaccination. The vast majority (95%, 11/216)) of the cases were reported within 3 weeks of vaccination. However, some cases were reported up to 41 days following vaccination.

Out of the 216 patients, 67 patients had either recovered, had recovered with sequelae or were recovering, 39 had not recovered and 3 deaths were reported.

Of the initial 216 cases, 92 cases described events of pericarditis including one fatality in a 72 year old woman. 42/92 (46 %) were reported in female patients and 49/92 (53%) were reported in male patients. Half of the cases of pericarditis occurred following the first dose.

Of the initial 216 cases, 108 cases described events of myocarditis and 16 cases reported events of both Pericarditis and Myocarditis for a total of 124 cases reporting an event of myocarditis including 3 fatalities (a 19 year old male patient, a 49 year old male patient and an 81 year old woman). The vast majority of the myocarditis cases were reported in male patients. Furthermore, the majority of the myocarditis cases were reported following the second dose.

The MAH further assessed the 108 cases of myocarditis based on a recent publication by Bonaca et al defining an approach to the diagnosis of myocarditis. When applying Bonaca's definitions, the MAH found 8 definite cases of myocarditis, 10 probable cases and 21 possible cases for a total of 39 cases out of 124 cases being categorized as having some degree of certainty in diagnosis of myocarditis.

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In the Monthly Safety report #6 (DSTS# 253419)²⁰, Pfizer retrieved 495 reports of myocarditis and pericarditis (up to May 25, 2021). Of the 495, there were 260 cases of myocarditis (all assessed as serious), 73 met a certainty in diagnosis of myocarditis when assessed based on the Brighton's Collaboration (BC) diagnostic certainty criteria. 18 cases Eighteen (18) cases were classified as BC Level 1 (confirmed), 24 cases as BC level 2 (probable), 31 cases as BC level 3 (possible).

The majority of the confirmed, probable and possible myocarditis case reports were in younger age groups below 39 years of age (48/73; 66%). None had a fatal outcome. There were more males than females. 2 cases assessed as possible myocarditis were from Canada.

*Canadian cases**Canada vigilance database/CAEFISS database*

Reports from the CAEFISS database up to May 2021 showed a statistical signal in all 5 statistical signal detection methods used to assess safety data.

As of June 21, 2021, 66 cases of myocarditis and/or pericarditis have been reported to the Canadian databases following the mRNA vaccines (51/66 Pfizer). Of the 66 patients, 9 have fully recovered, 14 were recovering and 28 had not yet recovered. These cases are currently being assessed for causality. At least one case (male patient, 25 year-old) met the Brighton Collaboration case definition level 1 of definite myocarditis. The data is also being analyzed to assess emerging patterns relating to time onset, age/sex patterns.

News reports

On June 23, 2021, the Toronto Sun reported that SickKids Hospital has seen “approximately five” cases of myocarditis in youth following vaccination and at least 2 children at McMaster Children's Hospital²¹.

*Causality Assessment**International Cases**Israel*

The Israel Ministry of Health confirmed a probability for a possible link between the second vaccine dose and the onset of myocarditis among young men aged 16 to 30. This link was found to be stronger among the younger age group, 16 to 19, compared to other age groups. This link

²⁰ HC6-024-e243022 (253419 - Response to MHPD Request dated 2021-06-07) - Summary Monthly Safety Report 6 30-APR-2021 through 31-May-2021

²¹ SickKids reports seeing post-vaccine myocarditis in kids | Toronto Sun

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became weaker the older the vaccinated individual is. In most cases myocarditis took the form of mild illness that passed within a few days.

United States

As per the data from the CDC in the United States most confirmed cases have occurred mostly in male adolescents and young adults age 16 years or older, more often after getting the second dose than after the first dose of one of the mRNA vaccine and the condition is typically seen within several days after COVID vaccination. These cases are rare in the context of global immunization and millions of vaccine doses administered.

Switzerland (Swissmedic)

Spontaneous reports from Switzerland

- 5 million doses administered (as at the start of June 2021)
- Reported cases up to May 27, 2021:
 - 12 reports: Myocarditis (2), Perimyocarditis²² (4), Pericarditis (6)
 - Reporting rate 1:400,000 vaccine doses
 - Women (3), Men (8), Unk (1)
 - Average age s 47 (range 18-70)
 - PfizerBionTech (4), Moderna (7), Unk (1)
 - After D1 (9), after D2 (3)
 - Time to onset 8.75 days (range 1-28 days)
 - 5/12 patients had a history of relevant illnesses (chronic kidney disease, kidney transplant, myelodysplastic syndrome, recurrent pericarditis (now with reported pericarditis after vaccination).
 - 1/12 death reported (67 yo, M, pre-existing heart disease and renal failure requiring dialysis)
 - *As can be ascertained from the documentation, most of the other patients experienced a fairly mild episode, or else the final details on the outcome of the illness are not yet available.*

Conclusion

- Whether a causal link actually exists between the mRNA vaccines and these reactions is currently classed as *unclear internationally in view of the low reporting rate, the low background incidence of the disease and the clinical complexity of the reported cases.*
- In any case, healthcare professionals should consider this tentative diagnosis when symptoms that are compatible with a myocarditis/pericarditis, but were not caused by other heart diseases, occur in individuals shortly after a vaccination.

²² With overlaps between these clinical presentations

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- Swissmedic will provide further information or introduce risk minimisation measures without delay if any new aspects come to light.

Singapore (HAS) published on June 11, 2021(Expert Committee on COVID-19 Vaccination)²³

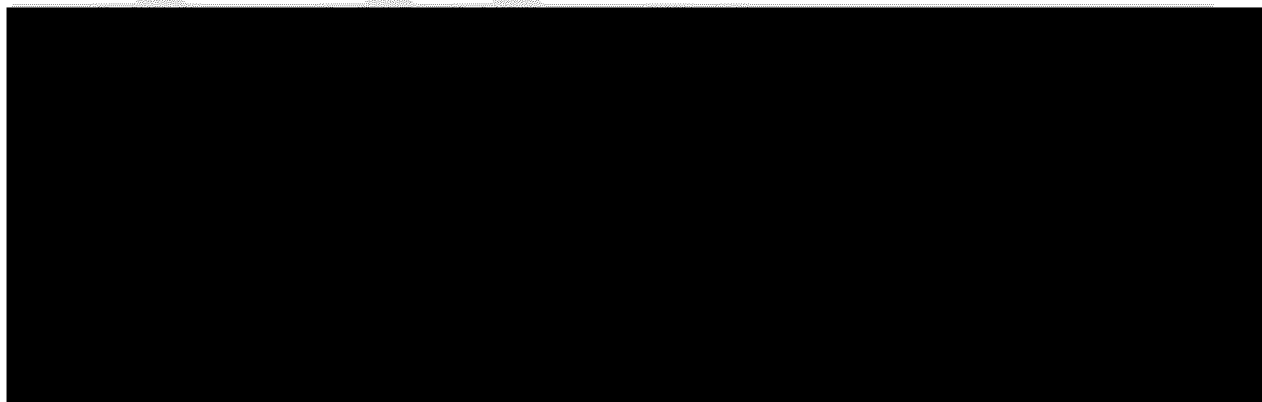
- Increased occurrences of myocarditis and pericarditis after the second dose observed in Israel and US in males below the age of 25 years.
- Risk estimated at 1.6 case per 100000 doses in the US, comparable to the risk of anaphylaxis observed in Singapore
- To date no observed incremental risk of myocarditis and pericarditis after the first dose of vaccine

Spontaneous reports from Singapore

- 4 reports in young men
- Age range 18 to 30 years
- At the upper end of the expected range for this age group, based on background incidence rates
- Most cases occurred after a few days of the 2nd dose (D2)
- All have recovered or have been discharged well from hospital

Conclusion

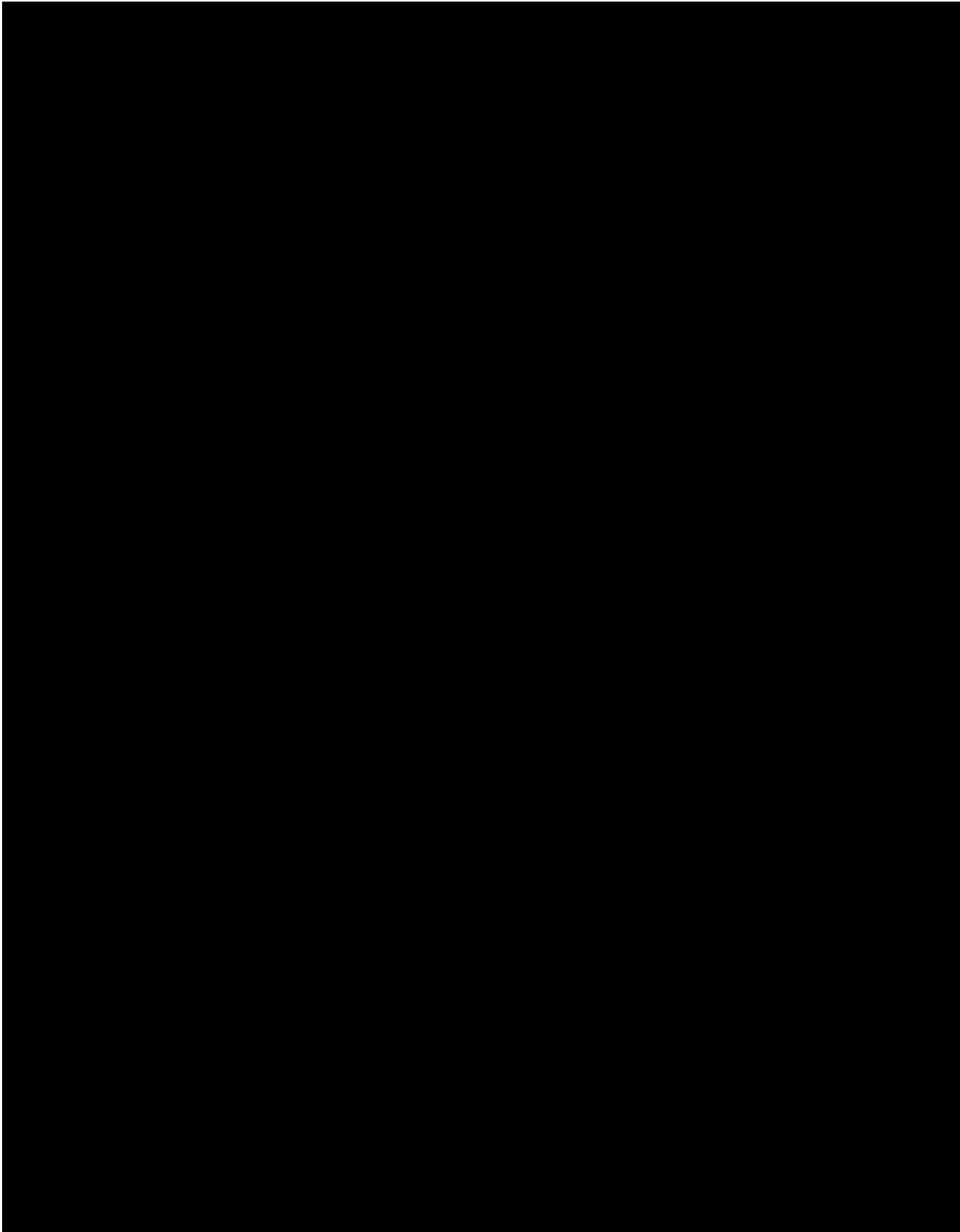
- While further studies and investigations are on-going, the currently available data suggests that there may be a very small risk of myocarditis and pericarditis after the second dose of an mRNA vaccine, particularly in young men.
- As a precaution, EC19V recommends that vaccinated persons, in particular adolescents and younger men, should avoid strenuous physical activity for one week after their second dose. During this time, they should seek medical attention promptly if they develop chest pain, shortness of breath or abnormal heartbeats
- EC19V will continue to monitor the available data

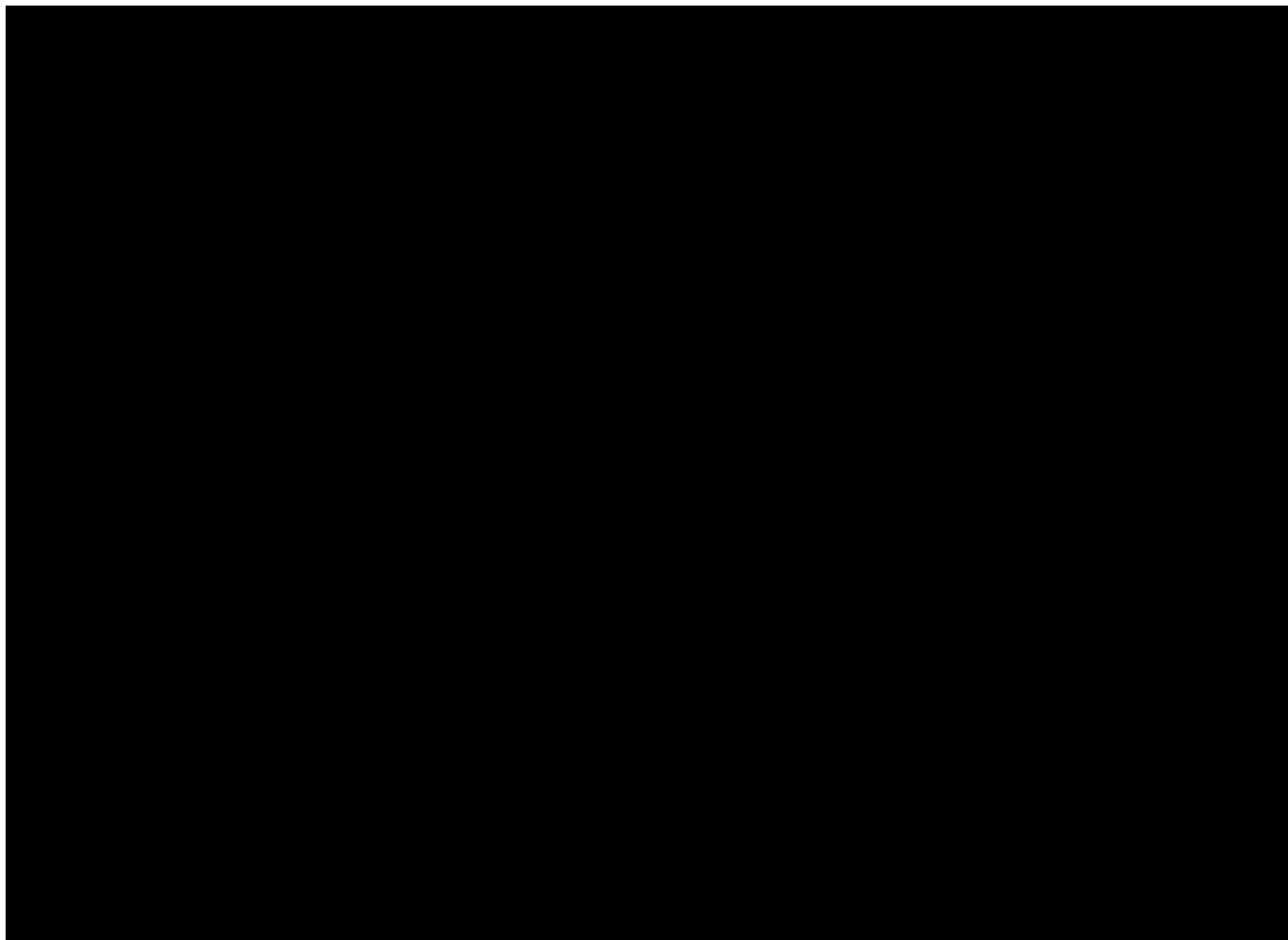


²³ [MOH | News Highlights](#)

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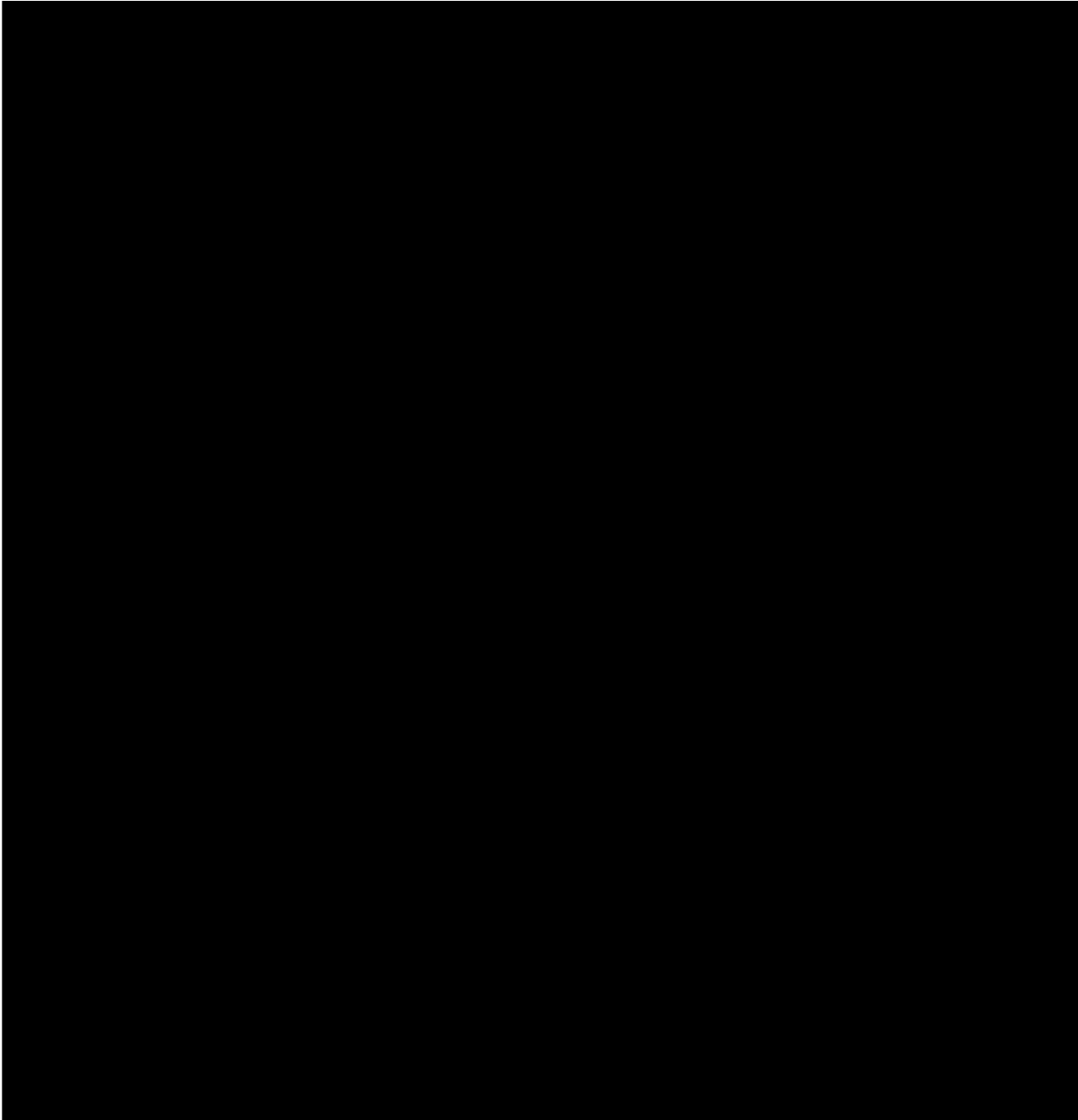
EMA PRAC meeting (meeting held on June 07, 2021)

- EMA data: based on Eudravigilance data assessment including an Observed/Expected analysis of myocarditis; a statistically disproportionate reporting was observed which was estimated to be 5 times higher in younger populations for all COVID vaccines for the signal of myocarditis. The signal was stronger in male patients; however, a signal was also detected in female patients in the younger age groups.
- The EMA PRAC decided to initiate a safety signal regarding this risk with accelerated timelines.
- During the meeting, Israel shared their estimate incidence data: estimated incidence of myocarditis in the 16 to 19 years of age following vaccination is about 1 case in 6000 vaccinated individuals.
- Signal to go ahead separately from MSSR (with shorter timelines to be able to have maximal regulatory impact)-considerations to terms will be taken into account (myocarditis and or pericarditis)

End of Confidential Information

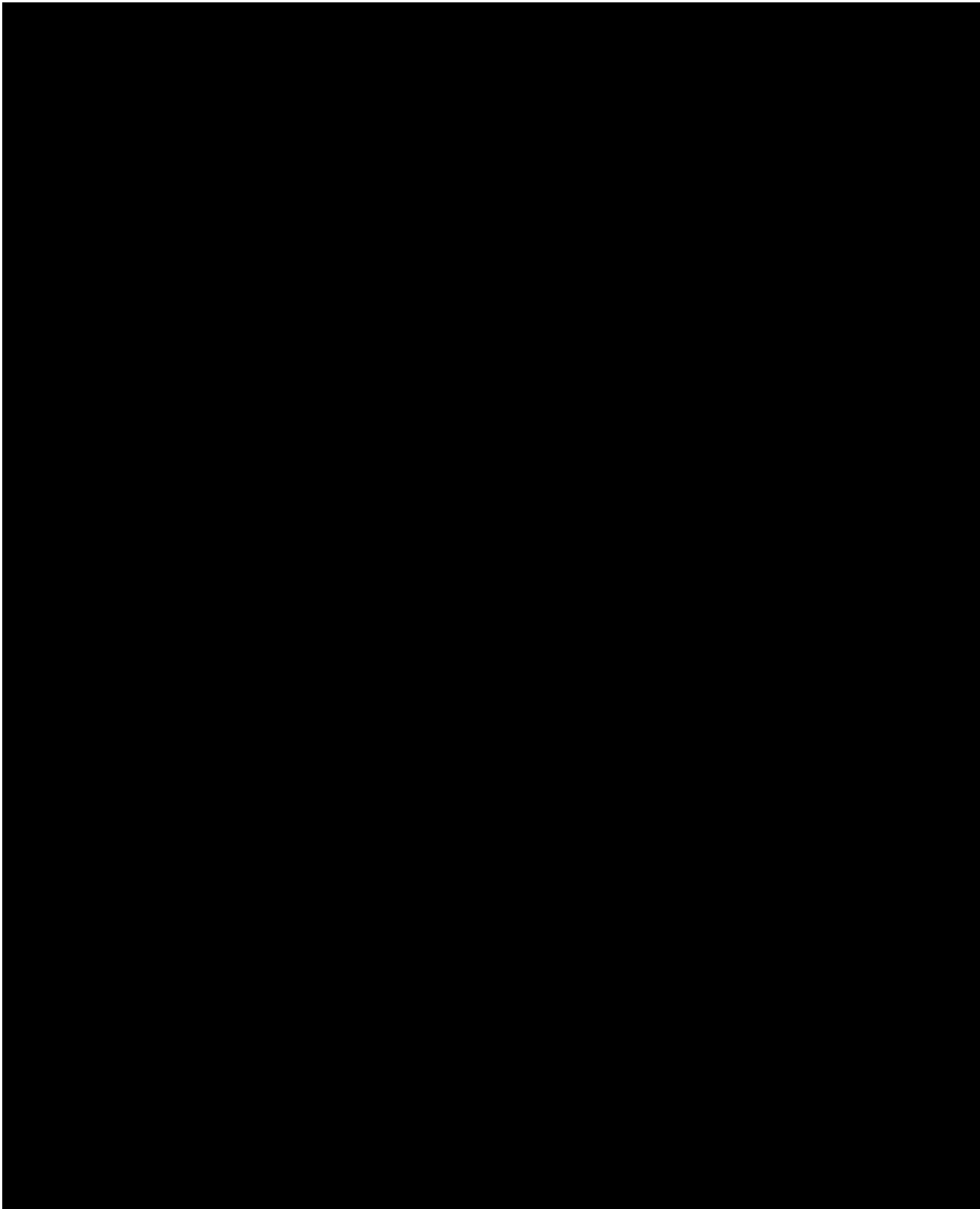
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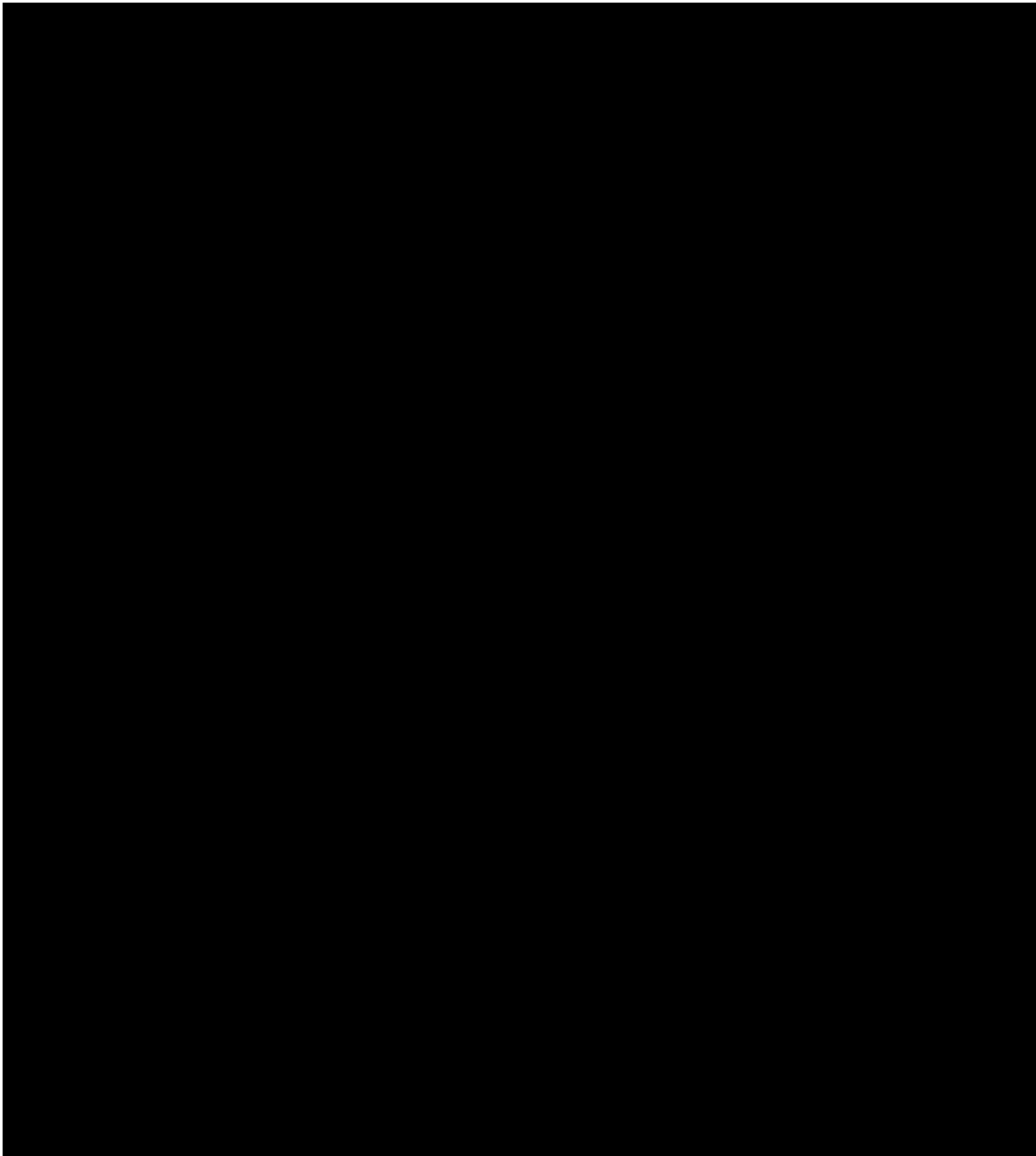
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²⁴ Laufer-Perl M, Havakuk O, Shacham Y, et al. Sex-based differences in prevalence and clinical presentation among pericarditis and myopericarditis patients. *Am J Emerg Med.* 2017;35(2):201-205. doi:10.1016/j.ajem.2016.10.039

²⁵ Slide 29 (dataset up to June 11, 2021, Tom Shimabukuro, MD, MPH, MBA) from the Advisory Committee on Immunization Practices, June 23, 2021 ACIP June 23, 2021, CDC COVID-19 Vaccine Task Force

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Scientific and medical literature

Analysis of Individual Case reports found in the literature

The patterns from international reporting have been also confirmed in at least 8 case reports/series published in the scientific and medical literature in the last 2 weeks. 8 case reports of potential interest for myocarditis were retrieved from an ongoing literature search.

1. Symptomatic Acute Myocarditis in Seven Adolescents Following Pfizer-BioNTech COVID-19 Vaccination (*Marshall et al, 2021*)²⁷

Summary

- 7 male patients (14 to 19 years old) (US)
- Myocarditis or myopericarditis 2-4 days after D2
- 6/7 no history of COVID-19 infection or another viral cause of inflammation
- Reported Symptoms: chest pain (7), fever (5), shortness of breath, fatigue, pain in both arms, nausea, vomiting, headache, anorexia and weakness
- Diagnosis: elevated troponin levels/abnormal electrocardiogram/cardiac MRI results
- Treatment: NSAIDs only (3), IV immune globin and corticosteroids (4)
- All recovered (within 2-6 days)
- Note (authors): Myocarditis onset shorter than myocarditis onset linked to smallpox vaccine
- Conclusion (authors): *Causality not established but temporal association with vaccination, striking similarity in the clinical and laboratory presentations raise the possibility for such a relationship*

2. Myocarditis after SARS-CoV-2 Vaccination: A Vaccine-induced Reaction? (*D'Angelo et al, 2021*)²⁸

Summary

- 30 year old male (Italy)
- Myocardio-pericarditis 72 hours after D2 (given 21 days after D1)

²⁶ Israel reports link between rare cases of heart inflammation and COVID-19 vaccination in young men | Science | AAAS ([sciencemag.org](https://www.sciencemag.org))

²⁷ Marshall M, Ferguson ID, Lewis P, et al. Symptomatic acute myocarditis in seven adolescents following Pfizer-BioNTech COVID-19 vaccination. *Pediatrics*. 2021; doi: 10.1542/peds.2021-052478 ([Case report](#))

²⁸ Case report. Myocarditis after SARS-CoV-2 Vaccination: A Vaccine-induced Reaction?

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- Tested negative for COVID-19, family history negative for rheumatological or genetic diseases
- Diagnosis: MRI/ECG and laboratory results
- Treatment: bisoprolol and acetylsalicylic acid, prednisolone
- Cardiac specific troponin levels progressively decreased, discharged home 7 days after hospitalization
- Conclusion (authors): *in our case, we speculate that adverse reaction against the COVID-19 vaccine was responsible for the development of myocarditis due to its temporal relationship. However, substantial evidences other than temporal aspects still need to be provided to demonstrate the causality, such as histologically proven cases of autoimmune myocarditis following vaccination.*

3. In Depth Evaluation of a Case of Presumed Myocarditis Following the Second Dose of COVID-19 mRNA Vaccine (Muthukumar et al, 2021)²⁹

Summary

- 50 year-old healthy male
- Presumptive diagnosis of myocarditis 3 days after Dose 2 (Moderna)
- Conclusion (authors): *The case does not prove a causal association between the vaccine and the observed myocarditis-like syndrome. However, ischemic injury and other potential causes of acute myocardial injury were excluded, as were other potential infectious causes of myocarditis, and there was no evidence of systemic autoimmune disease. The lack of evidence for upregulation of IL17 cytokine, combined with the increased NK cell numbers observed in the case patient, could suggest a distinct vaccine-associated immunophenotype with a high likelihood for rapid recovery. However, it is not clear whether the observed differences reflect a potential (causal) pathologic immune response or rather appropriate healing responses to myocardial inflammation*

4. Myocarditis Temporally Associated with COVID-19 Vaccination (Rosner et al, 2021)³⁰

Summary

- 7 male patients (US) below 40 years of age
- 6 patients received mRNA vaccines (Moderna or Pfizer)
- Myocarditis 3-7 days post vaccination
- Symptoms: acute onset chest pain
- Diagnosis: elevated troponin, ECG and cardiac magnetic resonance
- Medical history: None had evidence of an active viral illness or autoimmune disease and 6/7 had negative PCR testing. Assessment of COVID19 serology was obtained for 6/7 patients, with 4/6 showing presence of spike protein IgG antibodies.
- Treatment varied and included beta-blocker and anti-inflammatory medication
- Outcome: all recovered/symptoms resolved following 3±1 days

²⁹ Case report. Presumed Myocarditis Following the Second Dose of COVID-19 mRNA Vaccine

³⁰ Case-series (7 patients). Myocarditis after COVID-19 Vaccination

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- Conclusion (authors): *Our series of 7 male COVID-19 vaccination recipients who presented with myocarditis-like illness supports a potential causal association with vaccination given the temporal relationship, clinical presentation and CMR findings. The clinical course of vaccine-associated myocarditis-like illness appears favorable, with resolution of symptoms in all patients. Given the potential morbidity of COVID-19 infection even in younger adults, the risk-benefit decision for vaccination remains highly favorable.*
5. Myocarditis after BNT162b2 and mRNA-1273 Vaccination (Larson & Ammirati et al, 2021)³¹
Summary:
 6. scientific letter: Garcia et al, case report: ‘Acute myocarditis after administration of the BNT162b2 vaccine against COVID-19’
 7. Ammirati et al, case report ‘Temporal relation between second dose BNT162b2 mRNA Covid-19 vaccine and cardiac involvement in a patient with previous SARS-COV-2 infection’.

3. Summary

Conclusion



³¹ [Myocarditis after BNT162b2 and mRNA-1273 Vaccination | Circulation \(ahajournals.org\)](#)

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4. Considerations:

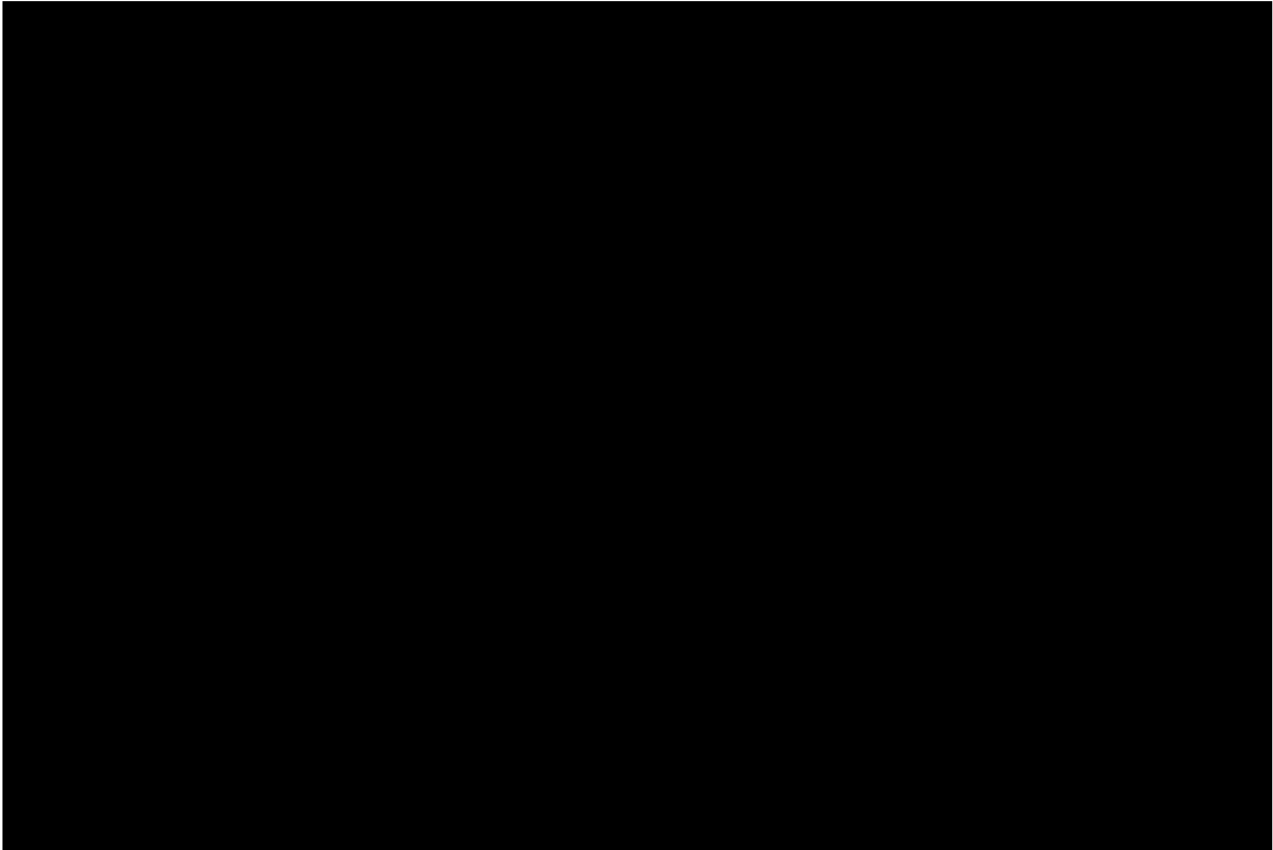
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5. Recommendations:

[Redacted]

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6. Managers

Scientific Medical

☐☐

Recommend for approval

Comment: (Include any concerns regarding differences in Scientific and/or medical opinion.)

7. Director

Agree: ☐

Disagree: ☐

Comment: (recommend either a formal Dissent process or written justification for agreement or disagreement with a recommendation from the manager(s) clearly stating what the Director is agreeing or disagreeing with.)

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8. References:

DRAFT

From: [Hunt, Melissa \(HC/SC\)](#)
Sent: 2021-07-09 6:35 AM
To: [Salem, Myriam \(HC/SC\)](#)
Subject: RE: 253419_Pfizer BioNTech SMSR 6_2021-07-07_0.1.docx
Attachments: 253419_Pfizer BioNTech SMSR 6_2021-07-07_0.1_MHcomment.docx

Hi Myriam,

Here are my comments for this first round. After this it can be uploaded and shared with the usual suspects (Saj, me, Tonja), for the next round of review.

Thank you!!

Melissa

From: Salem, Myriam (HC/SC) <myriam.salem@canada.ca>
Sent: 2021-07-07 6:07 PM
To: Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>
Cc: Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>; Rose, Jhona (HC/SC) <jhona.rose@canada.ca>
Subject: 253419_Pfizer BioNTech SMSR 6_2021-07-07_0.1.docx

Hi Melissa,

Please find attached the first draft of the Pfizer MSR 6 for your review.

I apologize for the delay.

Thank you,
Myriam

Marketed Health Products Directorate
Direction des produits de santé commercialisés

PERIODIC BENEFIT-RISK EVALUATION REPORT (PBRER) REVIEW
COMPREHENSIVE

PFIZER-BIONTECH COVID-19 VACCINE (BNT162B2, TOZINAMERAN)

SUMMARY MONTHLY SAFETY REPORT 6
29 APRIL 2021 TO 31 MAY 2021

CONTROL # 253419

(Including the MAH's Response to MHPD Requests under control number 253419)

Position Title: Director / Directeur(ice)
Bureau: Bureau of Biologics, Radiopharmaceuticals and Self-Care Products/ Bureau des produits biologiques, radiopharmaceutiques et auto-administratifs
Date: 07 July 2021
Signature: This document has been signed electronically using the Health Canada docuBridge system. / Ce document a été signé électroniquement à l'aide du système docuBridge de Santé Canada
Security – Classification – de sécurité: Protected B when completed / protégé B une fois terminé

EXECUTIVE SUMMARY

This Summary Monthly Safety Report 6 for the Pfizer-BioNTech COVID-19 Vaccine (BNT162B2, tozinameran) covers the period from 30 April 2021 to 31 May 2021.

Pfizer-BioNTech COVID-19 Vaccine (BNT162B2, tozinameran) is indicated for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS- CoV-2) in individuals 12 years of age and older.

The Pfizer-BioNTech COVID-19 Vaccine (BNT162B2, tozinameran) received marketing authorization in Canada under the *Interim Order Respecting the Importation, Sale and Advertising of Drugs for Use in Relation to COVID-19* (control no. 244906; 09 December 2020). The interim authorization of the Pfizer-BioNTech COVID-19 Vaccine is subject to Terms and Conditions that need to be met by the MAH. The Pfizer-BioNTech COVID-19 Vaccine has received temporary authorisation for emergency supply in 35 countries and conditional marketing authorisation approval in 43 countries globally.

The scope of this review is to assess the Summary Monthly Safety Report (SMSR) #6 for Pfizer-BioNTech COVID-19 Vaccine and determine whether the Terms and Conditions relevant to adverse events reporting are met by the MAH and to follow-up on issues that have been identified by the MHPD during the previous reporting interval.

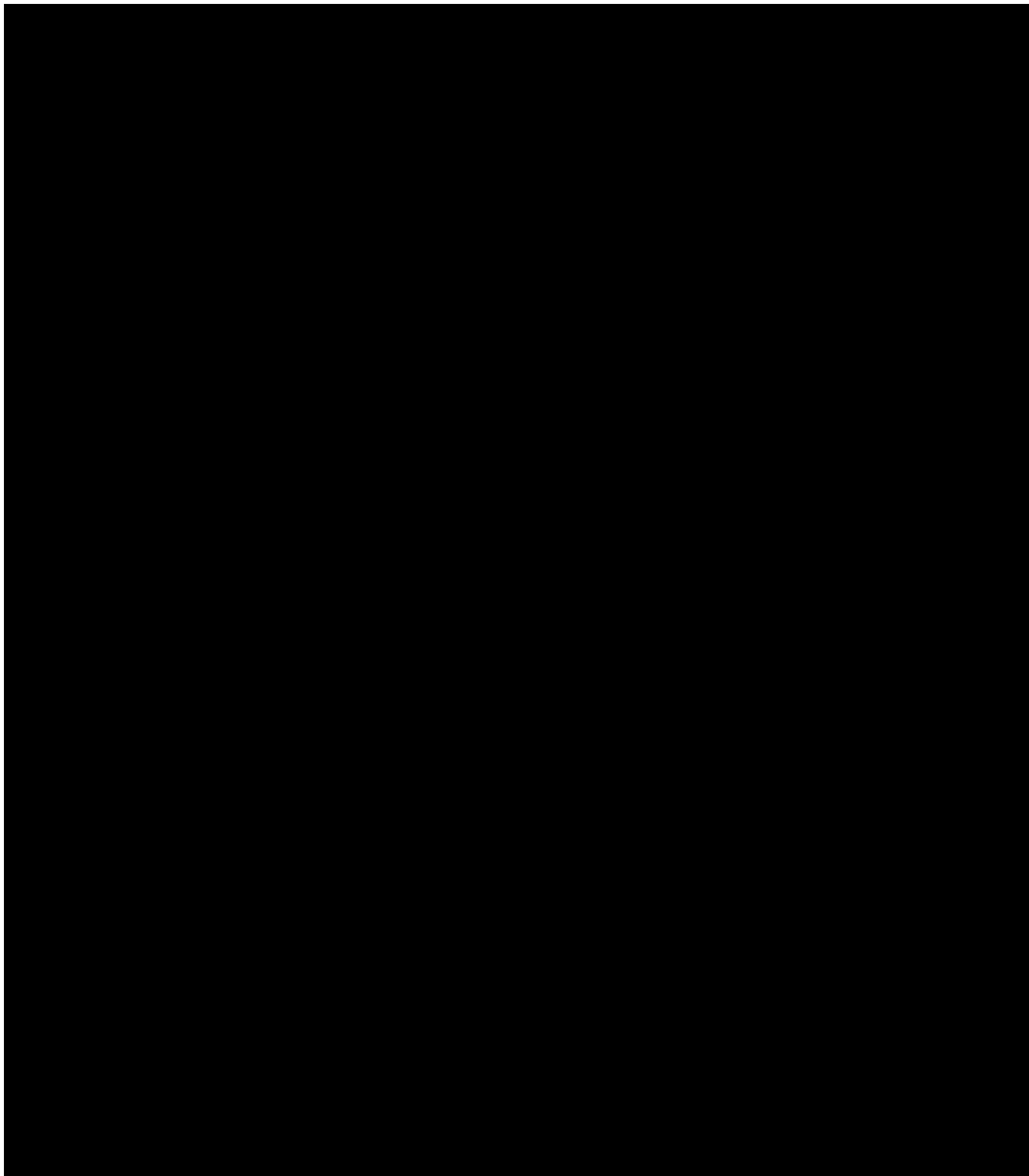
It was estimated that approximately 220,976,340 doses of the Pfizer-BioNTech COVID-19 Vaccine were shipped worldwide during the current reporting interval from 30 April 2021 to 31 May 2021. Of these, 10,452,780 doses were shipped to Canada. Of these, 8,884,863 were administered in Canada in the current interval.

A total of 47,174 cases with 174,446 adverse events were reported during this interval. Of the 47,174 cases

- a. 43 % of the reported cases were assessed as serious (20,288), 57% of the cases (26,885) were assessed as nonserious
- b. The majority of cases were from the United Kingdom (10,047) and the United States (8,975). Four hundred and twenty-three cases (423) were from Canada. One hundred and ninety (190) cases were in the previous interval period.
- c. Women represented the majority of the reported cases with 32,751 cases and men represented 11,506 cases (unknown data in 2,917 cases).
- d. The median age was 49.0 years old, with approximately a third of the cases 14,682 cases between the ages of 31 and 50 years old. Corresponding figures for age \leq 17 years old and age \geq 65 years old were 327 and 10,167, respectively (unknown age in 7,391 cases).
- e. Nine hundred and seventy-one (971) cases had a fatal outcome.

[REDACTED]

[REDACTED]



[REDACTED]

[REDACTED]

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1 INTRODUCTION

Control # / SAP #	253419
Canadian Market Authorization Holder (MAH) /Sponsor	Pfizer Canada ULC BioNTech Manufacturing GmbH
Product trade name	Pfizer-BioNTech COVID-19 vaccine
Active ingredient	BNT162B2, tozinameran
International Birth Date (IBD)	19 December 2020 (Switzerland)
Date Notice of Compliance (NOC) issued	09 December 2020
Date of marketing in Canada	14 December 2020
Type of document (PBRER, PSUR, ASR, PADERs, other)	Summary Monthly Safety Report
PBRER # and reporting interval	30 April 2021 to 31 May 2021
Last PBRER reviewed # and reporting interval	01 December 2020 to 31 December 2020 (control no. 248389) 01 January 2021 to 31 January 2021 (control no. 248783) 01 February 2021 to 28 February 2021 (control no. 250059) 01 March 2021 to 31 March 2021 (control no. 251805) 01 April 2021 to 29 April 2021 (control no. 251813)
Last RMP reviewed # and date	European RMP (EU RMP) version 2.0 (control no. 253040) Canadian addendum to the RMP dated May 2021
Date of current Canadian Product Monograph (CPM)	19 May 2021
Other documents submitted with the PBRER	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No Specify:
Foreign review available	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No Specify:
PBRER review type	Comprehensive

1.1 DESCRIPTION OF PRODUCT

BNT162b2 (or tozinameran) is a white to off-white frozen dispersion provided as concentrate for dispersion for injection (sterile concentrate) as multidose vial to be diluted before use. The multidose vial contains 6 doses of 0.3 mL after dilution if low dead-volume syringes and/or needles can be used to extract a 6th dose from a single vial. Each dose contains 30 micrograms of BNT162b2 as well as excipients.

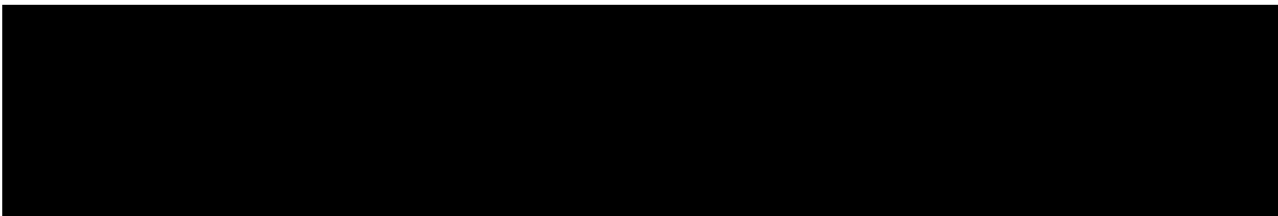
BNT162b2 is single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free *in vitro* transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2.

The nucleoside-modified mRNA is formulated in lipid nanoparticles, which enable delivery of the RNA into host cells to allow expression of the SARS-CoV-2 S antigen. The vaccine elicits both neutralizing antibody and cellular immune responses to the spike (S) antigen, which may contribute to protection against COVID-19.

1.2 PRODUCT USE

1.2a. Authorized indications in Canada

Pfizer-BioNTech COVID-19 Vaccine (COVID-19 mRNA Vaccine) is indicated for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 12 years of age and older.

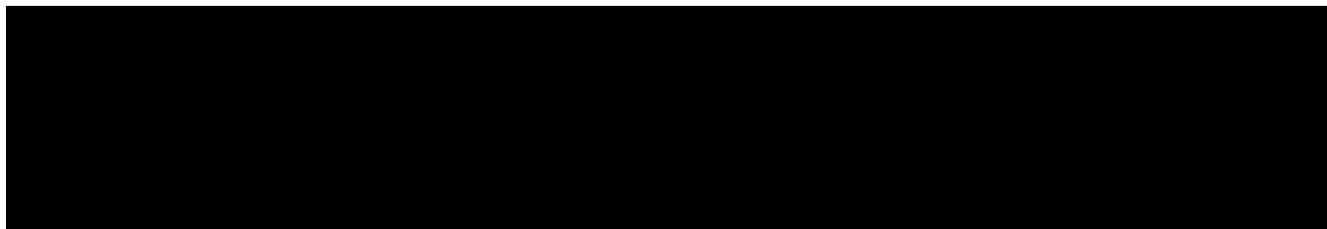


1.2b. Additional indications/uses noted in the PBRER

There is no additional indication noted in the Summary Monthly Safety Report.

1.3 IS THERE A PRE-MARKET SUBMISSION CURRENTLY UNDER REVIEW FOR THIS PRODUCT?

☒ No ☐ Yes



2 TRIGGER AND SCOPE OF THIS REVIEW

On 09 December 2020, the Pfizer-BioNTech COVID-19 Vaccine (BNT162B2, tozinameran) received marketing authorization in Canada under the *Interim Order Respecting the Importation, Sale and Advertising of Drugs for Use in Relation to COVID-19* (control no. 244906). The interim authorization of the Pfizer-BioNTech COVID-19 Vaccine is subject to terms and conditions that need to be met by the MAH. The terms and conditions relevant to adverse events reporting include the following:

Pfizer Canada ULC is required to submit monthly safety reports for the period of the Interim Order authorization, unless otherwise determined by Health Canada. The monthly safety reports should be submitted within 15 days after the last day of a month, beginning after the first full calendar month after authorization. These reports should contain the following:

- Interval and cumulative number of reports (serious and non-serious), overall and by age groups and in special populations (e.g. pregnant women)
- Interval and cumulative number of reports per HLT and SOC
- Number of reports in Canada and Global
- Exposure data, stratified by country, age groups, race and ethnicity
- Changes to reference safety information in the interval
- Ongoing and closed signals in the interval
- List of adverse events of special interest including the Safety Platform for Emergency Vaccines list and RMP safety concerns (including the additional missing information): reports – numbers and relevant cases, including time-to-onset and O/E analyses
- Fatal reports – numbers and relevant cases, including observed/expected analyses
- Vaccination failure / lack of efficacy (including confirmed and suspected cases) and errors – number relevant cases
- Potential interaction with other vaccines/concomitant treatments-number and relevant cases
- Summary outcomes of some of the routine pharmacovigilance activities (as presented in the EU RMP Part III and applied in the Canadian context) should be included for the purpose of rapid signal detection and communication activities. Summary of all ongoing studies can be included in the first six-month scheduled PBRER, unless a safety signal is identified that requires immediate regulatory action.
- Risk/benefit considerations

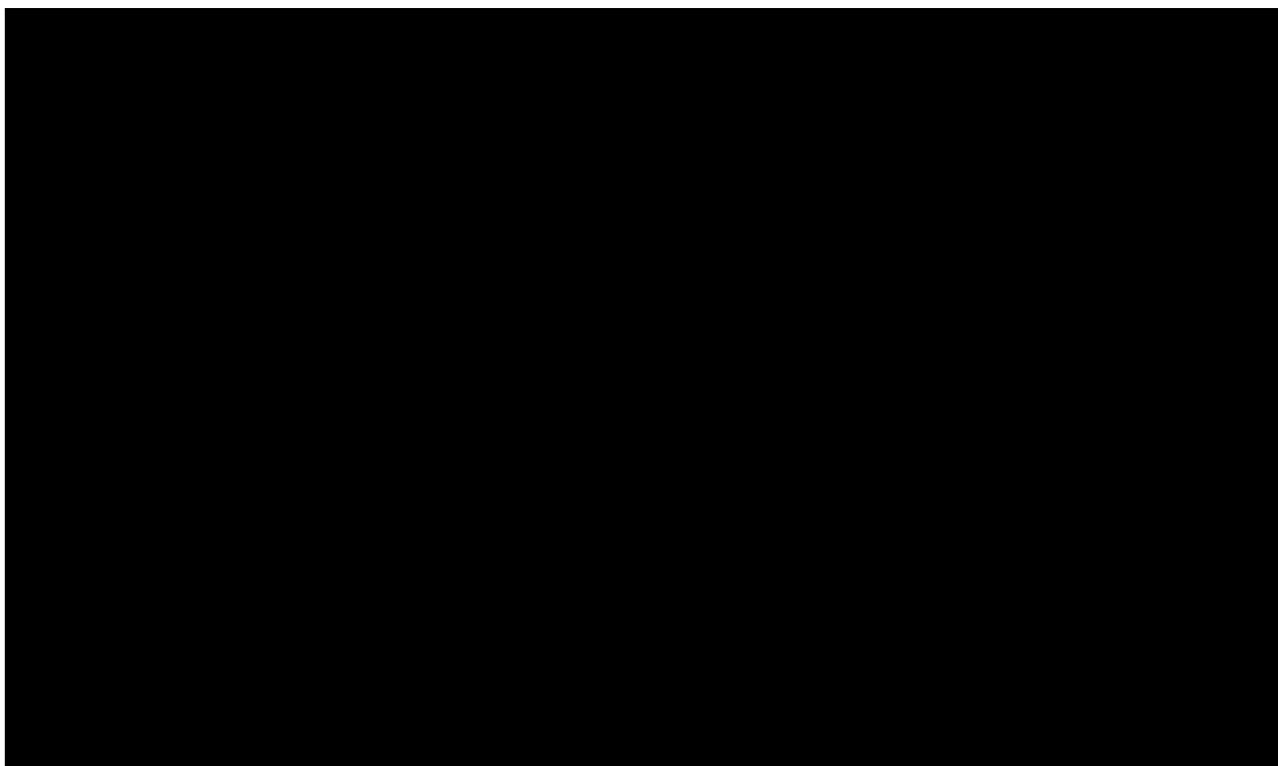
The scope of this review is to assess the current Summary Monthly Safety Report (SMSR) for the Pfizer-BioNTech COVID-19 Vaccine and determine whether the MAH meets the terms and conditions relevant to adverse event reporting (as listed immediately above) and to follow-up on issues that the MHPD identified during the previous reporting interval.

3 ACTIONS TAKEN IN THE REPORTING INTERVAL FOR SAFETY REASONS**3.1 HAVE ACTIONS TAKEN FOR SAFETY REASONS BY THE MAH OR REGULATORY AUTHORITIES BEEN REPORTED?**

☒ Yes ☐ No

Current interval:

No action was reported in the current interval.

Late Breaking information:**4 CHANGES TO THE REFERENCE SAFETY INFORMATION (RSI)**

The RSI for this SMSR is the BNT162b2 Core Data Sheet (CDS) Version 4.0 dated 19 May 2021, in effect at the end of the reporting period.

The previous BNT162B2 CDS Version 3.0 dated 20 April 2021 was also in effect during the reporting period. The MAH updated the CDS version 3.0 on 19 May 2021 to include: Asthenia, Lethargy, Decreased appetite, Hyperhidrosis and Night sweats as adverse drug reactions in Section 4.8 Undesirable effects, and the addition of warning text for Vaccine stress-related responses (including Dizziness, Fainting, Palpitations, Increases in heart rate, Alterations in blood pressure, Feeling short of breath, Tingling sensations, Sweating and/or Anxiety) in Section 4.4 Special warnings and precautions for use.

5 ESTIMATED EXPOSURE AND USE PATTERNS

It is estimated that approximately 639,868,710 doses of the Pfizer-BioNTech COVID-19 Vaccine were shipped worldwide through 31 May 2021, corresponding to approximately 542,013,978 doses administered cumulatively. During the current reporting period (from 30 April 2021 through 31 May 2021) approximately 220,976,340 doses were shipped worldwide corresponding to approximately 188,860,682 doses administered.

In Canada, 20,120,880 doses were shipped cumulatively, corresponding to approximately 17,102,748 doses administered including 8,884,863 doses administered during the reporting period compared to 3,309,696 doses administered in the previous interval.

6 DATA FROM PBRER SUMMARY TABULATIONS AND DATABASE SEARCHES

6.1 ADVERSE REACTION CODING DICTIONARY

The MedDRA version 24.0 was used to code adverse events/reactions during this reporting interval.

6.2 CUMULATIVE SUMMARY TABULATIONS OF SERIOUS ADVERSE EVENTS FROM CLINICAL TRIALS

Adverse events/reactions reported from clinical trials are discussed throughout this report.

6.3 CUMULATIVE AND INTERVAL SUMMARY TABULATIONS OF ADVERSE REACTIONS FROM POST-MARKETING DATA SOURCES

Cumulative number of cases from post-market experience (up to 31 May 2021):

The MAH received 167,956 reports from post-marketing data sources for Pfizer-BioNTech COVID-19 Vaccine through 31 May 2021. Of these, 1142 case reports were from Canada including 423 in the current interval.

Interval number of cases from post market experience (30 April 2021 up to 31 May 2021):

The MAH retrieved 47,174 cases (containing 174,446 events) in the current reporting interval. Of these, 423 cases were from Canada

MedDRA PTs reported in $\geq 2\%$ * Cases in the current interval/cumulative and relevant Canadian labelling

MedDRA SOC MedDRA PT	AEs (AERP%) (interval) N = 47174	AEs (AERP%) N = 167956	CPM Labelling (Y/N)
Blood and lymphatic system disorders			
Lymphadenopathy ^a	1914 (4.06%)	8382 (4.99%)	Y
Cardiac disorders			
Tachycardia	1093 (2.32%)	3596 (2.14%)	Y (partially labelled: fast heartbeat in the context of an allergic reaction, palpitations in the context of myocarditis)
Gastrointestinal disorders			
Nausea ^a	5053 (10.71%)	19303 (11.49%)	Y
Diarrhoea ^a	1786 (3.79%)	6879 (4.10%)	Y
Vomiting ^a	1664 (3.53%)	6253 (3.72%)	Y
General disorders and administration site conditions			
Fatigue ^a	7076 (15.00%)	28432 (16.93%)	Y
Pyrexia ^a	7341 (15.56%)	29507 (17.57%)	Y (fever)
Chills ^a	4990 (10.58%)	20176 (12.01%)	Y
Vaccination site pain ^a	4875 (10.33%)	18829 (11.21%)	Y
Pain ^a	2968 (6.29%)	12683 (7.55%)	Y
Malaise ^a	2968 (6.29%)	12683 (7.55%)	Y (feeling unwell)
Asthenia ^a	3460 (7.33%)	10855 (6.46%)	Y (weakness)
Drug ineffective ^b	1030 (2.18%)	4545 (2.71%)	
Feeling abnormal	4545 (2.71%)	3399 (2.02%)	Y (partial labelling: feeling unwell)
Immune system disorders			
Anaphylactic reaction ^a	758 (2.46%)	1965 (1.79%)	Y
Infections and infestations			
COVID-19 ^b	1898 (4.02%)	7063 (4.21%)	Y
Herpes Zoster	1243 (2.63%)	2234 (1.33%)	N
Musculoskeletal and connective tissue disorders			
Myalgia ^a	5531 (11.72%)	21315 (12.69%)	Y (muscle pain)
Pain in extremity ^a	4103 (8.70%)	15661 (9.32%)	Y
Arthralgia ^a	4282 (9.08%)	16204 (9.65%)	Y (joint pain)
Nervous system disorders			
Headache ^a	11689 (24.78%)	40612 (24.18%)	Y
Dizziness	4039 (8.56%)	13267 (7.90%)	Y

MedDRA SOC MedDRA PT	AEs (AERP%) (interval) N = 47174	AEs (AERP%) N = 167956	CPM Labelling (Y/N)
Paraesthesia	1366 (2.90%)	5337 (3.18%)	N (will be included in RSI)
Hypoaesthesia	1103 (2.34%)	3722 (2.22%)	N
Respiratory, thoracic and mediastinal disorders			
Dyspnoea ^c	1883 (3.90%)	7337 (4.37%)	Y (partially labelled: shortness of breath as part of the case definition of Covid-19)
Cough ^c	1413 (3.00%)	4434 (2.64%)	Y (partially labelled: shortness of breath as part of the case definition of Covid-19)
Oropharyngeal pain	1126 (2.39%)	3408 (2.03%)	N
Skin and subcutaneous tissue disorders			
Rash ^a	1791 (3.80%)	6121 (3.64%)	Y
Pruritus ^a	1949 (4.13%)	3845 (3.51%)	Y
Sensitive skin	1737 (3.68%)	2429 (1.45%)	N
Erythema ^a	1332 (2.82%)	4354 (2.59%)	Y (partially labelled: Redness/local reaction)
Urticaria	1002 (2.12%)	3275 (1.95%)	N
Total number of events	56829	223114	

6.4 CANADIAN ADVERSE REACTION DATA

6.4.1 Was a general search of the Canada Vigilance Database done?

☒ Yes ☐ No

6.4.2 If YES, indicate the Canada Vigilance reference #/date of online search, search strategy, results, and discuss the data

The Marketed Health Products Directorate (MHPD) performs daily Canada Vigilance searches for adverse reaction reports associated with Pfizer-BioNTech COVID-19 Vaccine. Adverse reaction reports are assessed independently by a scientific evaluator and a medical evaluator.

During the reporting interval of 01 April 2021 to 30 April 2021, 326 adverse reactions reports were recorded for the Pfizer-BioNTech. Of these adverse reactions, reports 7 were fatal. All these fatal reports were in patients aged 54, 58, 65 72, 72, 91, 91, 4 males, 1 female. Co-reported PTs include cerebral hemorrhage (2), pulmonary embolism, headache, myocardial infarction (2), cerebrovascular accident, and sudden death .

OTHER SAFETY DATABASES SEARCHES

The Canadian Adverse Events Following Immunization Surveillance System (CAEFISS) is a federal, provincial and territorial public health post-market vaccine safety surveillance system. CAEFISS is managed by the Public Health Agency of Canada (PHAC).

Up to and including 25 June 2021, 8570 adverse events following immunization (AEFIs) were reported to the Canada Vigilance Program and CAEFISS in Canada.¹ Of these 1884 were serious.

¹ <https://health-infobase.canada.ca/covid-19/vaccine-safety/>

Start of Confidential Information

Reports from the CAEFISS database up to July 05, 2021, as analyzed by the PHAC showing a statistical disproportional signal in all 5 statistical signal detection methods (included below):

AEFI's of interest (Pfizer/BioNTech COVID-19 vaccine)																				
Vaccination	AEFI	Pfizer Vaccine/AEFI events	Other vaccine/AEFI events	Proportional reporting ratio (PRR)	95% lower confidence interval (LCI)	95% upper confidence interval (UCI)	Chi-square statistic (Yates correction)	Chi-square expected cell frequency of less than 10	Chi-square expected cell frequency of less than 5	Reporting Odds Ratio (ROR)	Information Component (IC)	95% lower credibility interval (LCI)	95% lower credibility interval (LCI)	95% lower confidence interval (LCI)	95% upper confidence interval (UCI)	PRR signal flag	Chi-square signal flag	disproportionality flag	IC signal flag	ROR signal flag
Pfizer/BioNTech	Anaphylaxis	613	835	4.5728	4.1448	5.045	1043.94	1041.41	0	5.2330	1.61119	1.47783	1.70805	4.7372	5.514	1	1	1	1	1
Pfizer/BioNTech	Anaphylaxis (Bighorn Collaboration levels 1-3)	84	25	15.9452	10.0584	25.282	247.61	247.61	0	18.2177	2.35178	1.91702	2.62965	10.1573	25.773	1	1	1	1	1
Pfizer/BioNTech	Other allergic reactions	1322	7247	1.1862	1.0840	1.191	27.09	26.83	0	1.2195	1.5724	1.05946	2.2323	1.1280	1.505	1	0	0	1	1
Pfizer/BioNTech	Bell's Palsy	127	151	6.0384	4.7425	7.888	273.77	270.78	0	8.2199	181677	152313	2.02897	4.8803	7.980	1	1	1	1	1
Pfizer/BioNTech	Seizures	78	219	2.2184	1.7172	2.868	38.93	37.88	0	2.2450	91856	54123	1.19572	1.7295	2.914	1	1	1	1	1
Pfizer/BioNTech	Anaesthesia	108	31	21.2377	14.2952	31.730	468.41	461.07	0	21.9043	2.45282	2.13123	2.88493	14.6570	32.735	1	1	1	1	1
Pfizer/BioNTech	Paraesthesia	678	2194	1.9536	1.7871	2.092	261.57	260.64	0	2.1484	77529	64849	86740	1.9531	2.359	1	0	0	1	1
Pfizer/BioNTech	Other neurological diagnosis	1050	4773	1.3833	1.3071	1.464	118.22	117.75	0	1.5339	39333	29193	46701	1.4240	1.665	1	0	0	1	1
Pfizer/BioNTech	Arrhythmia	57	150	2.7821	2.0903	3.703	53.31	51.87	0	2.8154	1.14515	73988	1.43636	2.1083	3.783	1	1	1	1	1
Pfizer/BioNTech	Thrombocytopenia	35	47	4.6383	2.3988	7.175	57.43	55.03	0	4.8735	1.92368	1.02098	1.93412	3.0129	7.249	1	1	1	1	1
Pfizer/BioNTech	Vomiting	216	1072	1.2550	1.0889	1.448	3.79	3.54	0	1.2700	27638	105207	43993	1.0334	1.478	1	0	0	1	1
Pfizer/BioNTech	Diarrhea	191	896	1.3277	1.1402	1.546	13.28	12.96	0	1.3458	34393	10477	51723	1.1485	1.580	1	0	0	1	1
Pfizer/BioNTech	Platelet disorders	32	44	4.5235	2.8768	7.133	51.11	48.76	0	4.5681	1.56112	97947	1.97941	2.6888	7.201	1	1	1	1	1
Pfizer/BioNTech	Transverse myelitis	7	14	3.1143	1.2578	7.711	6.70	5.17	1	3.1183	1.13918	11398	1.9916	1.2578	7.731	1	1	1	0	1
Pfizer/BioNTech	Adenopharyngolymphadenopathy	212	574	2.3005	1.9725	2.682	111.31	116.17	0	2.3906	86303	73300	1.12450	2.0254	2.788	1	1	1	1	1
Pfizer/BioNTech	Embolic and thrombotic events	176	94	11.6620	9.101	14.944	303.46	306.11	0	12.2017	2.22124	1.97189	2.40167	9.4750	15.713	1	1	1	1	1
Pfizer/BioNTech	Cerebrovascular accidents	30	13	14.3735	7.5046	27.530	111.04	108.39	1	14.4944	2.24175	1.63294	2.67335	7.5412	27.794	1	1	1	1	1
Pfizer/BioNTech	Transient cerebrovascular events	13	3	26.9305	7.6950	94.671	61.04	55.51	1	27.0333	2.31477	1.37530	2.35786	7.7139	85.083	1	1	1	1	1
Pfizer/BioNTech	Pulmonary embolism	53	6	85.0191	23.6688	127.834	266.50	260.15	1	55.8144	2.62676	2.17046	2.95360	23.8760	123.832	1	1	1	1	1
Pfizer/BioNTech	Myocardial infarction	12	3	24.9143	7.0340	86.247	55.12	49.71	1	24.9331	2.27523	1.30053	2.34674	7.0494	88.611	1	1	1	1	1
Pfizer/BioNTech	Coagulopathies and bleeding diatheses	15	50	1.6666	1.0505	3.324	4.67	3.93	1	1.8722	70747	16350	130886	1.0502	3.337	1	0	0	0	1
Pfizer/BioNTech	Vascular haemorrhagic disorders	89	423	1.2522	1.0312	1.619	4.97	4.66	0	1.2395	31069	104049	56379	1.0314	1.637	1	0	0	0	1
Pfizer/BioNTech	Cardiac failure	12	1	74.7430	3.7213	374.566	67.13	60.77	1	74.3660	2.44322	1.48458	3.11072	3.7471	576.880	1	1	1	1	1
Pfizer/BioNTech	Myocarditis	45	21	13.3470	7.9605	22.370	163.95	159.41	1	13.5000	2.24020	1.74445	2.59437	8.0333	22.650	1	1	1	1	1
Pfizer/BioNTech	Haemorrhage	4	4	6.2286	1.5584	24.894	8.78	6.01	1	6.2343	1.46561	1.27334	2.56480	1.5585	24.833	1	1	1	0	1
Pfizer/BioNTech	Acute kidney injury	3	6	9.3423	3.3274	26.233	26.63	23.10	1	3.3535	1.85330	74434	2.64465	3.3300	26.322	1	1	1	1	1
Pfizer/BioNTech	Chilblains	5	0	-	-	-	31.15	24.34	1	1	2.20541	64423	3.19101	-	-	0	0	0	1	0
Pfizer/BioNTech	Cryoglobulinemia	12	42	4.7456	3.0001	7.507	53.04	51.40	0	4.7707	1.57103	1.00810	2.31612	3.0130	7.573	1	1	1	1	1
Pfizer/BioNTech	Tinnitus	27	55	3.0577	1.9317	4.840	25.15	23.57	0	3.0730	1.21529	87324	1.69343	1.9352	4.677	1	1	1	1	1
Pfizer/BioNTech	Sensorineural hearing loss	18	34	3.2975	1.8643	5.832	18.88	17.17	1	3.3089	1.26578	47241	1.81749	1.6668	5.685	1	1	1	1	1

[REDACTED]

End of Confidential Information

7 SIGNIFICANT FINDINGS FROM STUDIES OR OTHER SOURCES DURING THE REPORTING PERIOD

The SMSR did not include significant findings from completed and ongoing clinical trials, non-interventional studies, non-clinical data, and other periodic reports.



8 LATE-BREAKING INFORMATION

The section was not provided in this SMSR.

Actions taken for safety reasons by regulatory agencies

Based on data collected following mass immunization, the FDA, the MHRA and Health Canada requested a labelling update on June 25, 2021, to include a warning statement regarding the risk of myocarditis and/or pericarditis following immunization with mRNA COVID vaccines. The Pfizer BioNtech CPM was updated on 30 June 2021.

Following the review of the EU-RMP V2.0 and Canadian Addendum (DSTS# 253040) on June 07, 2021, the MAH was also requested to include myocarditis and pericarditis in the Canadian risk management plan and update the pharmacovigilance plan accordingly.

Start of Confidential Information

The EMA will be requesting a similar update as was done in other jurisdictions as well as an update in the RMP following the July 05-08, 2021 PRAC meeting.

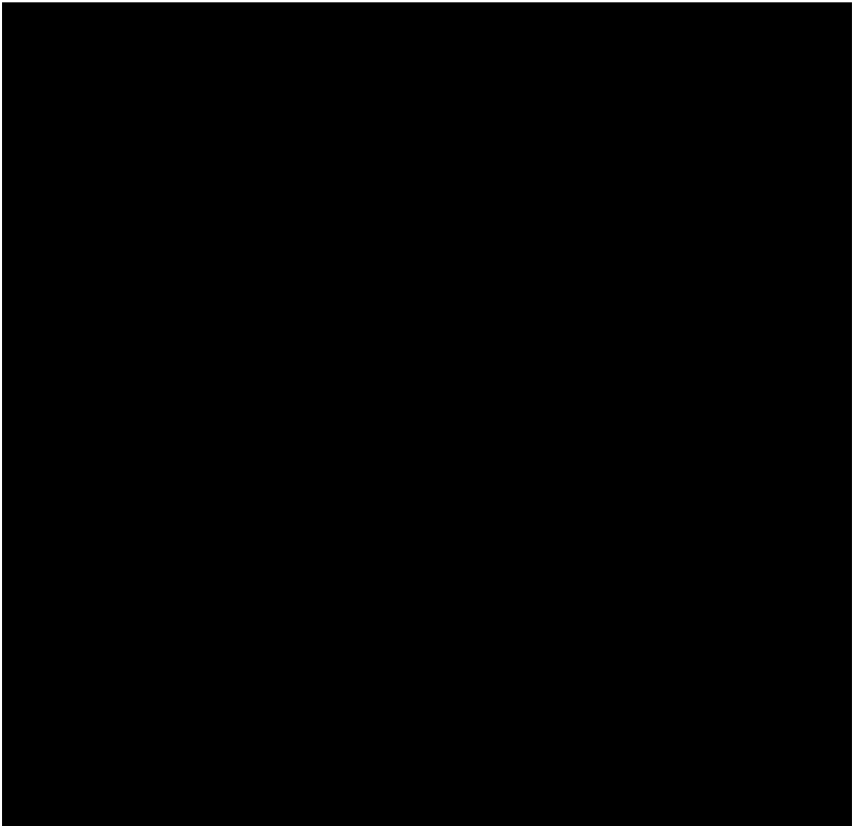
End of Confidential Information

9 OVERVIEW OF SIGNALS DISCUSSED BY THE MAH: NEW, ONGOING, OR CLOSED

During the reporting period, 10 signals were evaluated by the MAH and closed during the reporting period:

Safety topic	Safety Trigger/ MAH's Assessment	MHPD comments
Appendicitis	Health Canada request/ Evidence does not support a causal association- Signal closed	

Safety topic	Safety Trigger/ MAH's Assessment	MHPD comments
Dizziness	MHRA request/ The available information supports dizziness associated with the vaccination process (i.e. stress related response) but not a causal association with the vaccine itself at this time- Signal Closed	<p>From safety evaluation data reported under Appendix 3.7:</p> <p>Clinical trials</p> <p>The MAH notes that “Dizziness” was reported in 78 participants (0.4%) in the BNT162b2 group compared with 60 participants in the placebo group (AEs reported from Dose 1 to 1 month post dose 2 during the blinded controlled follow up period). Postural dizziness was reported by 2 (0.0%) BNT162b2 recipients and 1 (0.0%) placebo recipient.</p> <p>Post market cases (up to 30 April 2021) using MedDRA PT Dizziness</p> <ul style="list-style-type: none">a. A total of 15,260 cases were reported for BNT162b2.b. Median Age was 46. Most frequent reported age was between 31-50 years oldc. Approximately 40% of the cases occurred within the first 24 hours. Co-reported events were most commonly reactogenicity events. The most common were headache (2718), nausea (2097), asthenia (1216), and chills (1130)d. There were 8 events of dizziness with a fatal outcome. 4 cases with a latency of Day 0. Of these, 3 cases were in patients between 80-94 years of age with a medical history of neurological and cardiac manifestations), 1 case with a fatal outcome with latency of Day 2, a 27 year-old male experienced dizziness and vomiting blood 2 days after vaccination. <p>As per the Summary of the MAH’s assessment/conclusion: because dizziness is a term commonly used by patients to describe symptoms that are inconsistently defined, and based on the postauthorization reports, it is plausible that the dizziness experienced soon after vaccination is a potential manifestation of vaccination-related situational stress, anxiety and/or is confounded by the systemic reactogenicity experienced in the same time period. Cases of dizziness that described an inability to drive were relatively rare (11). Additionally, in the course of the Phase 2/3 clinical trials, events of dizziness were not meaningfully different in the active cohort (0.4%) compared to placebo cohort (0.3%).</p> <div></div>

Myocarditis/ pericarditis	Signal ongoing	<p>The MAH retrieved 495 reports of myocarditis and pericarditis (up to May 25, 2021). Of the 495, there were 260 cases of myocarditis (all assessed as serious), 73 met a certainty in diagnosis of myocarditis when assessed based on the Brighton’s Collaboration (BC) diagnostic certainty criteria. 18 cases Eighteen (18) cases were classified as BC Level 1 (confirmed), 24 cases as BC level 2 (probable), 31 cases as BC level 3 (possible).</p> <p>The majority of the confirmed, probable and possible myocarditis case reports were in younger age groups below 39 years of age (48/73; 66%). None had a fatal outcome. There were more males than females. 2 cases assessed as possible myocarditis were from Canada.</p> <p>MAH’s assessment/conclusion: The rate at which these events are reported (even without applying the diagnostic certainty criteria) do not exceed the expected background rate. It should be noted that with the case information currently available, only 18 (6.9%) of the cases could be assessed as “confirmed cases” of myocarditis as per Brighton Collaboration criteria. It is worth noting that the incidence rate of myocarditis in COVID-19 infected patients is 2.3 out of 100 in a recovering population. Given the totality of the data, a causal association between the vaccine and myocarditis or pericarditis cannot be established. The MAH will continue to perform robust pharmacovigilance, follow up, and monitoring of this topic.</p> 
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Safety topic	Safety Trigger/ MAH's Assessment	MHPD comments
Abnormal behaviour/mental disorder	Japan PMDA/No validated signal	<p>The MAH did not provide the assessment regarding abnormal behaviour in the monthly safety report #6; however, the MAH concluded that the available data do not support this topic as a validated signal.</p>
Acquired Hemophilia	Request from France ANSM/No Validated Signal	<p>The MAH did not provide the assessment regarding acquired hemophilia in the monthly safety report #6; however, the MAH concluded that the available data do not support this topic as a validated signal. The MAH noted that the ANSM 15th PV report of AEs found 3 cases of acquired hemophilia since the start of vaccination and considered it as a potential signal. A review of the small number of post-authorization AE reports of acquired hemophilia was undertaken and this topic was determined not to be a validated signal.</p>
Acute disseminated Encephalomyelitis (ADEM)	PRAC request/No Validated Signal	<p>The MAH notes that ADEM has been described most frequently following measles mumps and rubella vaccinations, but at a lower incidence of ADEM after a wild-type measles encephalitis. Other reports of ADEM have been described both after H1N1 infection and H1N1 vaccination.</p> <p>Post-marketing cases</p>

		<p>-78 cases were reported including one case from a Pfizer-sponsored interventional study.</p> <p>-majority of cases (64/78) were medically confirmed.</p> <p>-Median reported age 51.5, mean 54.2 years</p> <p>- Of the 78 reports, 48 (61.5%) were reported as females, 29 (37.2%) as males, and in 1 (1.3%) case sex was not reported</p> <p>-Most cases were from the US (18) and UK (14), France and Spain (6 each)</p> <p>-Time to onset (reported in 58 cases) ranged between 2 to 21 days in 43 cases. 12 cases reported time to onset as the same vaccination day or day after. In 3 cases time to onset was reported as 22, 28 and 38 days post-vaccination.</p> <p>- Case outcome was reported as recovered/recovering/recovered with sequelae in 33 cases (42.3%), not recovered at time of reporting in 28 cases (35.9 %), and outcome was unknown in 11 cases (14.1%) .There were also 6 fatal cases (7.7%).</p> <p>-All cases were assessed according to BC criteria. None of the cases met BC level 1. 75 cases were assessed as follows:</p> <ul style="list-style-type: none">• 7 cases (9.2%) met level 2;• 11 cases (14.5%) met level 3;• 41 cases (55.3%) met level 4 (reported encephalitis/ADEM with insufficient evidence to meet the case definition);• 16 cases (21%) met level 5 (not a case of encephalitis/ADEM) <p>Among the 59 cases that met BC level 2,3 4, alternative explanations including previous disease/neurologic co-morbidities were reported.</p> <p>Of note, the MAH revised the observed to expected ratio based on a background rate of 5.3 per 100,000 person years to better align with the spontaneously reported case definition. In the previous SMR the MAH used a background rate of 0.1 from the ACCESS initiative.</p> <p>According to the MAH, given the totality of the available information, this review of the data did not support validation of a signal. Changes in the risk minimization measures or updates to the product information label are not warranted at this time. The benefit risk profile of the vaccine remains favorable. The topic will continue to be closely monitored.</p> <div></div>
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Safety topic	Safety Trigger/ MAH's Assessment	MHPD comments
Acute pancreatitis	Request from France ANSM/ No Validated Signal	<p>The MAH did not provide the assessment regarding acute pancreatitis in the monthly safety report #6; however, the MAH concluded that the available data do not support this topic as a validated signal. The MAH noted that the ANSM 14th PV report of AEs found 19 cases of acute pancreatitis since the start of vaccination and considered it as a potential signal. A review of the AE reports of acute pancreatitis was undertaken and this topic was determined not to be a validated signal.</p> <div></div>

Safety topic	Safety Trigger/ MAH's Assessment	MHPD comments
Guillain-Barre Syndrome	Request from France ANSM/No Validated Signal	<p>Post market cases</p> <p>The MAH retrieved 147 cases from their database (up to May 10, 2021):</p> <ul style="list-style-type: none"> -76 females and 67 males -Age range between 18 to 97 years, mean 59.3 years - Most of the cases were reported from US (36, 24.5%), United Kingdom (30, 20.4%) followed by Japan (12, 8.2%). -The outcome of the event was reported as not recovered at time of reporting in 53 cases (36.1%), as recovering/resolving in 53 cases (36.0 %), and as unknown in 36 cases (24.5%) and fatal in 5 cases (3.4%) - Time to onset ranged from same vaccination day to 63 days following vaccination, with the majority of cases reported within 7 days of vaccination. <p>All cases have been assessed according to BC criteria as follows:</p> <ul style="list-style-type: none"> • 4 case (2.7 %) met level 1 • 16 cases (10.8 %) met level 2 • 1 case (0.7 %) met level 3 • 116 cases (79 %) met level 4 • 9 cases (6.1 %) met level 5 • 1 case (0.7%) was referring to another vaccine <p>Medical history found confounding factors in 33 cases (cerebrovascular accident (2), Chronic inflammatory demyelinating polyradiculoneuropathy (4), autoimmune disease, HIV and Cancer (14), Covid-19 infection (3 cases), symptoms in 1 case were pre-existing vaccination.</p> <p>MAH's assessment/ conclusion: Most reported cases (79%) met level 4 of BC. Most cases meeting BC level 1 or 2 were confounded by preceding infection, implausible time to onset, symptoms pre-existing vaccination or GBS in the context of cerebral infarct. The upper limit of the 95% confidence interval for the observed to expected ratio did not exceed 1; therefore, a signal was not identified. Overall, given the totality of the available information, GBS is not considered to be a validated signal, changes in the risk minimization measures or updates to the product information label are not warranted at this time. The benefit risk profile of the vaccine remains favorable.</p>

Safety topic	Safety Trigger/ MAH's Assessment	MHPD comments
Menstrual cycle abnormalities	Request from Israel Ministry of Health/ No Validated Signal	<p>The MAH noted a review of menstrual terms from the clinical study data and from the postauthorization AE reports was undertaken. The available data did not support a validated signal.</p> <div></div>

Safety topic	Safety Trigger/ MAH's Assessment	MHPD comments
Transverse myelitis	Request from Australia TGA/ No validated signal	<p>The MAH noted several case reports describing transverse myelitis in temporal relationship with Coronavirus infection have been published. The reported time to onset was between 8 days to 3 weeks upon infection symptoms.</p> <p><u>Post-market (data as of 17 May, 2021)</u></p> <ul style="list-style-type: none"> -67 cases identified. All cases were assessed as serious. -51 females, 15 males, and in one case gender was not reported. -Age range between 21 to 84 years (mean 48, median 43) -Most of the cases were reported from UK (23, 34.3%), followed by United States (20, 29.9%). -The outcome of the event was reported as not recovered at time of reporting in 30 cases (44.8%) resolving/recovering in 25 (37.3%) and unknown in 15 cases (17.9%).. All cases have been assessed according to BC criteria as follows: <ul style="list-style-type: none"> • 0 cases (0%) met level 1 • 2 cases (3%) met level 2 • 5 cases (7.5%) met level 3 • 53 cases (79.1%) met level 4 • 7 cases (10.4%) met level 5 - Time to onset was reported for 34 cases and ranged from the same vaccination day to 21 days after vaccination. - Unadjusted observed to expected ratio (O/E) analyses were conducted for the 67 reported TM cases. The O/E ratio was above 1 for the 21-day risk window and below 1 for the no risk window, indicating there may be an increased risk of TM among recipients of the BNT162b2 vaccine. <p>MAH's conclusion/assessment: The E/O analysis showed a small increase over the 21 days risk window nevertheless, as described in the O/E analysis the 21-day risk window is particularly conservative as all observed cases are included in the numerator of the O/E ratio regardless of the days since vaccination dose, which will lead to an overestimation of the ratio if observed cases occurred outside of the risk window. In addition, the ACCESS background rate used to calculate the expected number of cases is derived from medical records coded as transverse myelitis or acute transverse myelitis while the observed cases were identified in the spontaneous reporting system using a broader search criteria (as specified in the method). Updates to the product information label is not warranted at this time.</p>

10 REVIEW OF NEW SAFETY INFORMATION

10.1 SUMMARY OF SAFETY CONCERNS

The summary of safety concerns for the Pfizer-BioNTech COVID-19 Vaccine can be found below. This summary includes ongoing safety concerns from both the European RMP (EU RMP) version 1.1 dated 15 April 2021, the US Pharmacovigilance Plan (PVP) version 0.4 dated 08 April 2021 and the South Africa RMP version 1.0 dated 24 March 2021.

Important identified risk	Anaphylaxis
Important potential risk	Vaccine-Associated Enhanced Disease (VAED), including Vaccine-Associated Enhanced Respiratory Disease (VAERD)
Missing information	Use in pregnancy and while breast feeding
	Use in immunocompromised patients
	Use in frail patients with co-morbidities (e.g., COPD, diabetes, chronic neurological disease, cardiovascular disorders, active tuberculosis)
	Use in patients with autoimmune or inflammatory disorders
	Interaction with other vaccines
	Long-term safety data
	Use in paediatric individuals <12 years of age
	Vaccine effectiveness

10.2 SUMMARY OF ADVERSE EVENTS OF SPECIAL INTEREST

The search criteria for the adverse events of special interest (AESIs) for the Pfizer-BioNTech COVID-19 Vaccine can be found in Appendix **Error! Reference source not found.** The list of AESIs takes into consideration AESIs from expert groups and regulatory authorities, including the Brighton Collaboration.

10.2.1 Adverse events of special interest (AESI)

Pfizer provided cumulative assessment for AESI(s) noted in the table below, and did not validate any signals or identify new risks emerging from their analysis. No further action was proposed, standard surveillance is applied.

AESI Category	MAH's assessment	MHPD comments
Anaphylactic Reactions <i>Search criteria:</i> <i>Anaphylactic reaction SMQ (Narrow and Broad, with the algorithm applied), selecting relevant cases according to BC criteria</i>	No signal	Anaphylaxis is labelled in the CPM under Warnings and Precautions. No new safety information based on the provided information, no further regulatory action is recommended at this time.


<p>Cardiovascular AESIs <i>Search criteria: PTs</i> <i>Acute myocardial infarction;</i> <i>Arrhythmia; Cardiac failure; Cardiac failure acute; Cardiogenic shock; Coronary artery disease; Myocardial infarction; Postural orthostatic tachycardia syndrome; Stress cardiomyopathy; Tachycardia</i></p>	<p>No signal</p>	<p>Number of cases: 1585 (3.4 % of the total PM dataset, compared to 2.8% in the previous reporting period) 1217 medically confirmed and 368 are non-medically confirmed; - age (n = 1502): ranged from 16 to 101 years (mean = 50.8 years, median = 46 years); -Subjects' age group (n = 1514): Adult36 (1088), Elderly (422) and Adolescent (4); -Reported relevant PTs: Tachycardia (1093), Arrhythmia* (177), Myocardial infarction* (170), Cardiac failure* (87), Acute myocardial infarction* (66), Cardiac failure acute* and Cardiogenic shock* (13 each), Coronary artery disease* and Postural orthostatic tachycardia syndrome* (10 each), Stress cardiomyopathy* (6). - Outcome:39 resolved/resolving (727), not resolved (182), fatal (119), resolved with sequelae (22) and unknown (596); -Median time to onset is 24 hours following vaccination.</p> <p>MAH's conclusion/assessment: No cardiovascular signals have emerged from the review of post-authorisation data. The review of cases and O/E analysis do not raise new concerns. Safety surveillance will continue.</p> <div></div>
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AESI Category	MAH's assessment	MHPD comments
COVID-19 AESIs <i>Search criteria: Covid-19 SMQ (Narrow and Broad) OR PTs Ageusia; Anosmia</i>	No signal	No new safety information based on the provided information, no further regulatory action is recommended at this time.
Dermatological AESIs <i>Search criteria: PT Chillblains; Erythema multiforme</i>	No signal	No new safety information based on the provided information, no further regulatory action is recommended at this time. There are currently a total of <u>11 cases</u> reported following the Pfizer BioNtech vaccine in the Canadian databases (report published July 5, 2021). Chillbains and Erythema multiform are closely monitored by the MHPD and PHAC and are included in the AESIs for COVID vaccines.

AESI Category	MAH's assessment	MHPD comments
Facial Paralysis <i>Search criteria: PTs</i> <i>Facial paralysis, Facial paresis, Oculofacial paralysis</i>	No signal	

² https://www.ema.europa.eu/en/documents/product-information/comirnaty-epar-product-information_en.pdf

³ <https://www.fda.gov/media/144413/download>

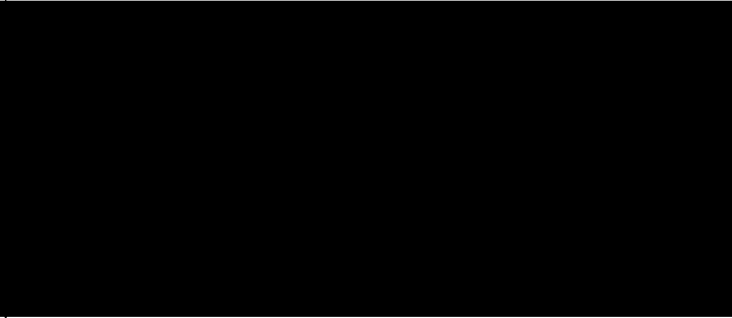
AESI Category	MAH's assessment	MHPD comments
<p>Haematological AESIs <i>Search criteria:</i> <i>Leukopenias NEC (HLT)</i> <i>OR Neutropenias (HLT)</i> <i>OR PTs Immune thrombocytopenia, Thrombocytopenia OR SMQ Haemorrhage terms (excl laboratory terms)</i></p>	No signal	<p>Most frequently reported relevant PTs (10 occurrences) include: Heavy menstrual bleeding (323), Contusion (227), Epistaxis (196), Thrombocytopenia* (186), Haemorrhage* (121), Vaginal haemorrhage (104), Vaccination site bruising (73), Petechiae (70), Intermenstrual bleeding (68), Immune thrombocytopenia* (57), Vaccination site haematoma (52), Haematoma (51), Purpura (46), Haematochezia (42), Vaccination site haemorrhage (41), Eye haemorrhage, Postmenopausal haemorrhage and Rectal haemorrhage (34 each), Conjunctival haemorrhage and Haematuria (27 each), Blood urine present (24), Ecchymosis, Haemoptysis and Internal haemorrhage (22 each), Gingival bleeding (21), Neutropenia (18), Gastrointestinal haemorrhage (15), Lymphopenia (14), Diarrhoea haemorrhagic, Haematemesis and Haemorrhage subcutaneous (13 each) and Blood blister, Leukopenia and Subdural haematoma (12 each)</p> 
<p>Musculoskeletal AESIs <i>Search criteria: PTs Arthralgia; Arthritis; Arthritis bacterial; Chronic fatigue syndrome; Polyarthrititis; Post viral fatigue syndrome; Rheumatoid arthritis</i></p>	No signal	<p>No new safety information based on the provided information, no further regulatory action is required at this time.</p>

AESI Category	MAH's assessment	MHPD comments
Neurological AESIs (including demyelination) <i>Search criteria:</i> <i>Convulsions (SMQ) (Broad and Narrow) OR Demyelination (SMQ) (Broad and Narrow) OR PTs Ataxia; Cataplexy; Encephalopathy; Fibromyalgia; Intracranial</i>	No signal	<p>Most frequently reported relevant PTs (≥ 5 occurrences) included: Seizure* (236), Neuropathy peripheral* (101), Epilepsy (84), Guillain-Barre syndrome* (60), Generalised tonic-clonic seizure* (38), Fibromyalgia* (30), Febrile convulsion* and Multiple sclerosis* (23 each), Trigeminal neuralgia (22), Status epilepticus (16), Optic neuritis* (15), Multiple sclerosis relapse* (13), Ataxia (12), Myelitis transverse* (11), Tongue biting (8), Polyneuropathy (7), Acute disseminated encephalomyelitis*, Aura, Meningitis*, Meningitis aseptic*, Partial seizures*, Seizure like phenomena (6 each), Clonic convulsion, Intracranial pressure increased and Petit mal epilepsy (5 each);</p> <p>6 serious cases were reported in Canada in the current interval.</p>
Hepatic AESIs <i>Search criteria: Liver related investigations, signs and symptoms (SMQ) (Narrow and Broad) OR PT Liver injury</i>	No signal	No new safety information based on the provided information, no further regulatory action is recommended at this time.
Immune-Mediated/Autoimmune AESIs <i>Search criteria: Immune mediated/autoimmune disorders (SMQ) (Broad and Narrow) OR Autoimmune disorders HLGTS OR PTs Cytokine release syndrome; Cytokine storm; Hypersensitivity</i>	No signal	No new safety information based on the provided information, no further regulatory action is recommended at this time.

<p>Pregnancy Related AESIs <i>Search criteria: PTs Amniotic cavity infection; Caesarean section; Congenital anomaly; Death neonatal; Eclampsia; Foetal distress syndrome; Low birth weight baby; Maternal exposure during pregnancy; Placenta praevia; Pre-eclampsia; Premature labour; Stillbirth; Uterine rupture; Vasa praevia</i></p>	<p>No signal</p>	<p>The MAH provided a cumulative analysis regarding the outcome of reported pregnancies.</p> <p>Cumulatively a total of 995 unique pregnancies were reported, 317 of which were received during the reporting interval.</p> <p>Overall, the majority (763) of these cases had insufficient information to conduct a meaningful medical assessment of causality (e.g., concomitant medications, trimester of exposure, pregnancy outcome, medical history). Of the 1036 cases reported cumulatively, 478 were assessed as serious. The most frequently reported pregnancy related events in these cases coded to the PTs Abortion spontaneous (187), Abortion missed (19), Foetal death (16), Premature baby (13), Foetal growth restriction (10), and Abortion (6).</p> <p>MAH’s conclusion: The review of the cases indicative of drug exposure during pregnancy did not reveal any new safety information.</p> <p>The MAH is conducting a post-authorization study (C4591015) to study the safety of the vaccine in pregnancy.</p> <div></div>
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AESI Category	MAH's assessment	MHPD comments
Renal AESIs <i>Search criteria: PTs Acute kidney injury; Renal failure.</i>	No signal	No new safety information based on the provided information, no further regulatory action is recommended at this time.
Respiratory AESIs <i>Search criteria: Lower respiratory tract infections NEC (HLT) OR Respiratory failures (excl neonatal) (HLT) OR Viral lower respiratory tract infections (HLT) OR PTs: Acute respiratory distress syndrome; Endotracheal intubation; Hypoxia; Pulmonary haemorrhage; Respiratory disorder; Severe acute respiratory syndrome</i>	No signal	No new safety information based on the provided information, no further regulatory action is recommended at this time.

AESI Category	MAH's assessment	MHPD comments
<p>Thromboembolic Events <i>Search criteria: Embolism and thrombosis (HLGT), excluding PTs reviewed as Stroke AESIs, OR PTs Deep vein thrombosis; Disseminated intravascular coagulation; Embolism; Embolism venous; Pulmonary embolism</i></p>	No signal	<p>Most frequently reported relevant PTs (≥5 occurrences) included: Pulmonary embolism* (588), Deep vein thrombosis* (442), Thrombosis (339), Thrombophlebitis superficial (65), Thrombophlebitis (53), Venous thrombosis limb (37), Embolism(36), Pulmonary thrombosis (35), Venous thrombosis (24), Retinal vein occlusion (21), Retinal artery occlusion and Portal vein thrombosis (17 each), Mesenteric vein thrombosis (14), Retinal vein thrombosis (13), Jugular vein thrombosis and Peripheral artery thrombosis (11 each), Pelvic venous thrombosis (10), Arterial thrombosis, Intracardiac thrombus, Ophthalmic vein thrombosis and Subclavian vein thrombosis (8 each), Coronary artery thrombosis (7), Embolism venous and Pulmonary artery thrombosis (6), Retinal artery thrombosis (5);</p> <p>There were 23 cases of thromboembolic events reported in the current interval in Canada</p> <div></div>

AESI Category	MAH's assessment	MHPD comments
Stroke <i>Search criteria: HLT Central nervous system haemorrhages and cerebrovascular accidents (Primary Path) OR HLT Cerebrovascular venous and sinus thrombosis (Primary Path)</i>	No signal	<p>Most frequently reported relevant PTs (≥ 5 occurrences) included:</p> <ul style="list-style-type: none"> o PTs indicative of Ischaemic stroke: Cerebrovascular accident* (308), Ischaemic stroke* (144), Cerebral infarction* (106), Cerebral venous sinus thrombosis* (35), Cerebral thrombosis* (22), Cerebral ischaemia (18), Embolic stroke (14), Thrombotic stroke* (9), Cerebral artery embolism, Cerebral venous thrombosis and Ischaemic cerebral infarction (8 each), Brain stem infarction and Cerebral artery occlusion (6 each) and Carotid artery occlusion, Carotid artery thrombosis, Cerebellar stroke, Cerebral artery thrombosis and Lacunar infarction (5 each); o PTs indicative of Haemorrhagic stroke: Cerebral haemorrhage* (93), Subarachnoid haemorrhage* (32), Haemorrhagic stroke* (18), Cerebral haematoma*, Haemorrhage intracranial* and Haemorrhagic transformation stroke (6 each); <p>8 cases were reported in Canada in the current interval.</p> 
Vasculitic Events <i>Search criteria: Vasculitides HLT</i>	No signal	No new safety information based on the provided information, no further regulatory action is required at this time.

10.3 SUMMARY OF SPECIAL SITUATIONS

10.3.1 Special situations

Overall, the MAH did not identify new safety signal from the evaluation of special situations (Death, Lack of Efficacy and Vaccine Interactions). : Causes of death most frequently reported (>2% of total fatal cases): Death (198), COVID-19 (76), Cardiac arrest (72), Sudden death (63), Dyspnoea (58), Pulmonary embolism (56), Cardio-respiratory arrest (49), Myocardial infarction (45), Vaccination failure (41), Pyrexia (39), COVID-19 pneumonia (35), Respiratory failure (34), Cerebrovascular accident, Drug ineffective (31 each), Cerebral haemorrhage, Pneumonia (29 each), Cardiac failure (23), and Vomiting (20).

11 EFFECTIVENESS STUDIES

As noted by the MAH, a statistically greater response was achieved in Study 2 in the adolescents 12 to 15 years of age compared to participants 16 to 25 years of age to demonstrate a non-inferior immune responses:

The geometric mean titers (GMT) ratio of the adolescents 12 to 15 years of age group to the participants 16 to 25 years of age group was 1.76, with a 2-sided 95% CI of 1.47 to 2.10, meeting the 1.5-fold non-inferiority criterion (the lower bound of the 2-sided 95% CI for the geometric mean ratio [GMR] >0.67) which indicates a statistically greater response in the adolescents 12 to 15 years of age than that of participants 16 to 25 years of age.

12 OTHER SAFETY CONCERNS AND FOLLOW-UPS

11.1. Responses to MHPD following the assessment of the April monthly safety report

In accordance with the Risk Management Plan Terms and Conditions, imposed under the Interim Order Respecting the Importation, Sale and Advertising of Drugs for Use in Relation to Covid-19, Pfizer Canada ULC is required to submit monthly safety reports for the period of the Interim Order authorization. As such, you are requested to submit the monthly safety report for the period of April 30, 2021 to May 31, 2021 including cumulative number of reports (serious and non-serious) and adverse events that occurred in Canada and globally for the Pfizer-BioNTech COVID-19 Vaccine (tozinameran) known to Pfizer Canada ULC and BioNTech Manufacturing GmbH. Actions for Pfizer Canada ULC and BioNTech Manufacturing GmbH stemming from the SMSR #5 review are to:

Comment 1

Discuss the need to submit a new Post-Authorization change – PM safety update and/or update the risk management plan regarding the following risks:

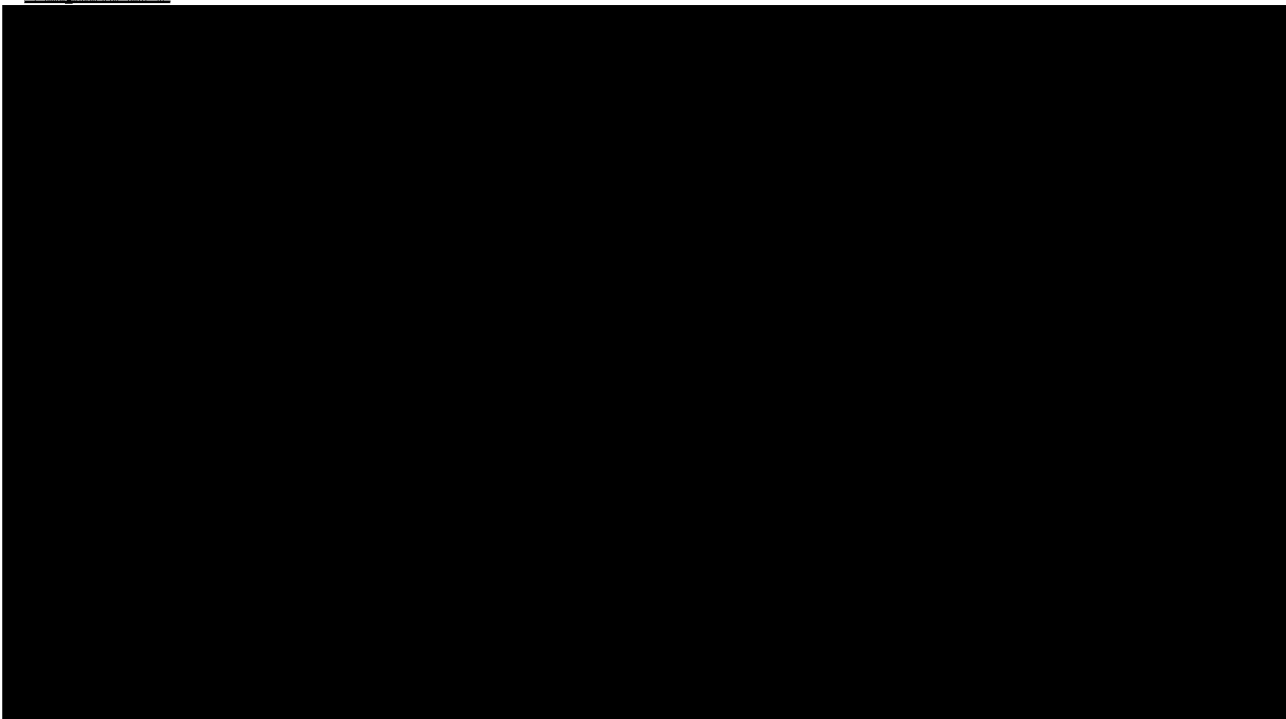
Facial paralysis /Bell's Palsy in association with the Pfizer-BioNTech COVID-19 Vaccine, based on the imbalance observed in the clinical trials, increase in frequency of reporting from the post-market data, and safety information captured in the EMASmPC and EUA USPI (including Bell's Palsy).

Myocarditis/Pericarditis in association with the Pfizer-BioNTech COVID-19 Vaccine- based on the following:

substantive number of cases that met the Bonaca criteria for definite, probable and possible myocarditis in the SMSR #5 most events are temporally related to the vaccination

Israel Ministry of Health¹ concluded a possible link between the second dose and the onset of myocarditis among young men (16-30), and that this link was highlighted to be stronger among the 16-19 younger age group.

that adolescents and the young adult population will soon be vaccinated in much larger numbers.

Response 1:**Comment 2**

Discuss the timeline for alignment of the Reference Safety Information and the Canadian Product Monograph for the following events: Asthenia, Lethargy, Decreased appetite, Hyperhidrosis, Night sweats and Paresthesia. In addition, address any plans to include labelling updates from other jurisdictions, such as facial swelling in people with a history of injections with dermal fillers recommended by the European Medicines Agency.

Response 2:**Comment 3**

In addition, please include the following in the next SMSR:

Provide an updated cumulative review of the following safety topics. Data should be stratified by sex, age, gender, dose 1 or dose 2 and assessed for causality using Brighton Collaboration Definition Criteria (or validated Definition Criteria). The observed and expected analyses should be included. An analysis of Canadian cases should be included. In addition, discuss the need for any potential amendment to the product monograph and/or the risk management plan and make, accordingly, a proposal for the changes to the relevant sections within this discussion.

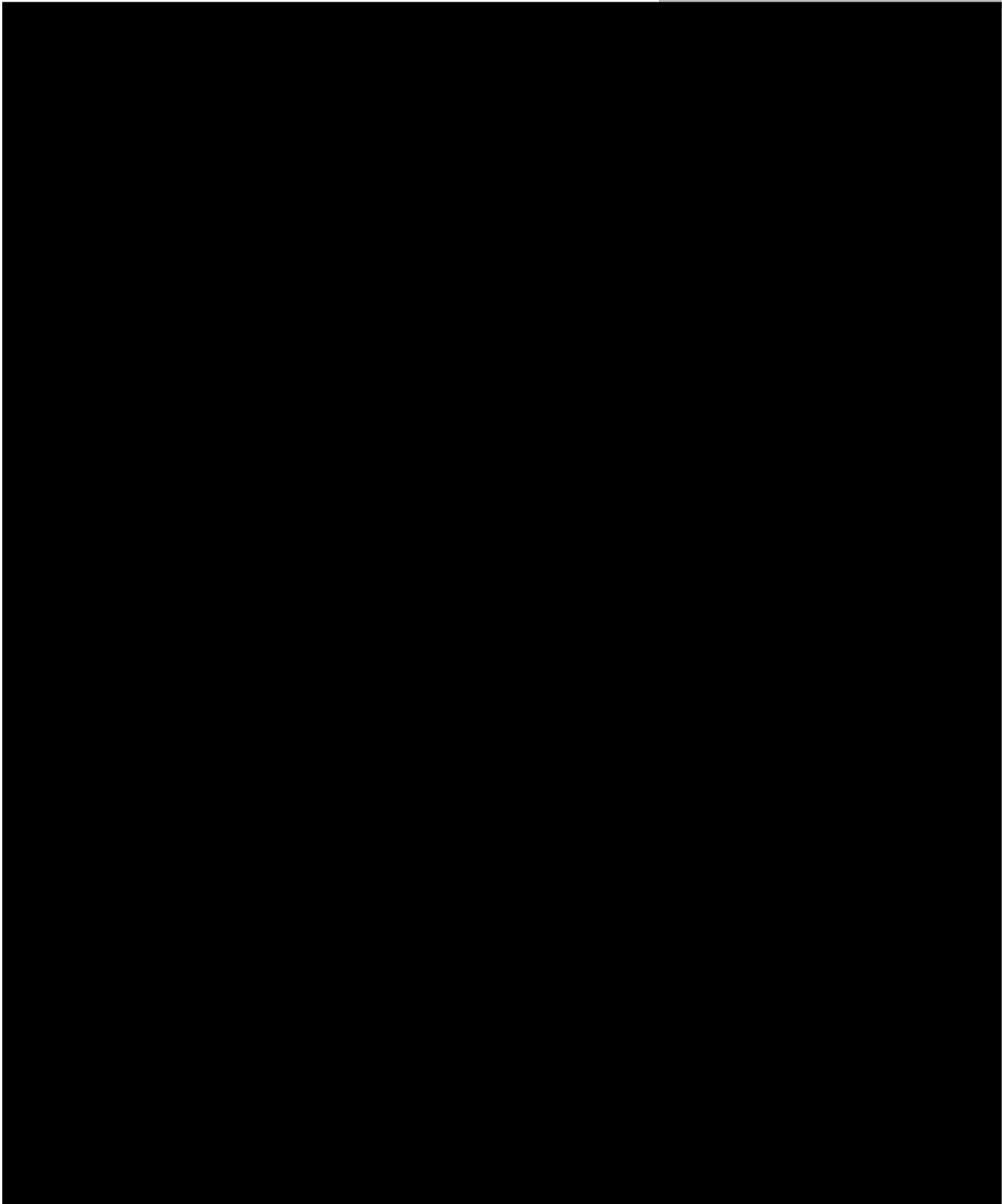
Cases of thrombosis with thrombocytopenia following vaccination with Pfizer BioNtech using appropriate SMQs to extract the cases including: thrombotic events with/without thrombocytopenia and thrombocytopenia without applying time limit specifications.

Cases of seizure following vaccination of Pfizer BioNtech vaccine. Search criteria should be included and encompass all generalized convulsive seizures following immunization.

Cases of hypertensive crisis with intracranial haemorrhage and provide a discussion regarding cases recently described in the literature.

Cases of hearing loss and trigeminal neuralgia, and provide a discussion regarding cases recently analyzed.

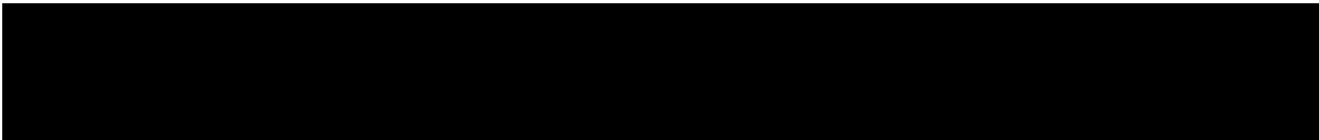
Response 3:



13 TERMS AND CONDITIONS

As stated in section 2, the Pfizer-BioNTech COVID-19 Vaccine is subject to terms and conditions that need to be met by the MAH. The compliance of the MAH to the terms and conditions relevant to adverse events reporting will be assessed below.

Terms and conditions	Met or not met
The monthly safety reports should be submitted within 15 days after the last day of a month, beginning after the first full calendar month after authorization.	
Interval and cumulative number of reports (serious and non-serious), overall and by age groups and in special populations (e.g. pregnant women)	
Interval and cumulative number of reports per HLT and SOC	
Number of reports in Canada and Global	
Exposure data, stratified by country, age groups, race and ethnicity	
Changes to reference safety information in the interval	
Ongoing and closed signals in the interval	
List of adverse events of special interest including the Safety Platform for Emergency Vaccines list and RMP safety concerns (including the additional missing information): reports – numbers and relevant cases, including time-to-onset and O/E analyses	
Fatal reports – numbers and relevant cases, including observed/expected analyses	
Vaccination failure / lack of efficacy (including confirmed and suspected cases) and errors – number relevant cases	
Potential interaction with other vaccines/concomitant treatments-number and relevant cases	
Summary outcomes of some of the routine pharmacovigilance activities (as presented in the EU RMP Part III and applied in the Canadian context) should be included for the purpose of rapid signal detection and communication activities. Summary of all ongoing studies can be included in the first six-month scheduled PBRER, unless a safety signal is identified that requires immediate regulatory action.	
Risk/benefit considerations	



14 COMPLIANCE ISSUES (GVP/GMP)

The section was not provided in this SMSR.

15 RECOMMENDATIONS

From Executive Summary

16 REFERENCES

The references are provided as footnotes and hyperlinks throughout the document.

17 APPENDICES

From: Coleman, Gina (HC/SC) <gina.coleman@canada.ca>
Sent: 2021-07-13 11:13 AM
To: Salem, Myriam (HC/SC)
Subject: RE: BRDD action required: Pfizer BioNtech vaccine Memo to BRDD Control number: 251813 and 253419

Thank you Myriam!

From: Salem, Myriam (HC/SC) <myriam.salem@canada.ca>
Sent: 2021-07-13 11:12 AM
To: Coleman, Gina (HC/SC) <gina.coleman@canada.ca>; Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>; Bouthillier, Leo (HC/SC) <leo.bouthillier@canada.ca>; Cherry, Elana (HC/SC) <elana.cherry@canada.ca>; Faraci, Maria (HC/SC) <maria.faraci@canada.ca>; HC.F ORA_COVID / BAR_COVID F.SC <hc.ora_covid-bar_covid.sc@canada.ca>; Raymond, Joel (HC/SC) <joel.raymond@canada.ca>; Ali, Osman (HC/SC) <osman.ali@canada.ca>
Cc: Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>; Rose, Jhona (HC/SC) <jhona.rose@canada.ca>; Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>
Subject: RE: BRDD action required: Pfizer BioNtech vaccine Memo to BRDD Control number: 251813 and 253419

Hi Gina,

RSI is the Reference Safety Information; however, I have changed it below to CDS (Core Data Sheet) in red.

Thank you,
 Myriam

From: Coleman, Gina (HC/SC) <gina.coleman@canada.ca>
Sent: 2021-07-13 11:07 AM
To: Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>; Bouthillier, Leo (HC/SC) <leo.bouthillier@canada.ca>; Cherry, Elana (HC/SC) <elana.cherry@canada.ca>; Faraci, Maria (HC/SC) <maria.faraci@canada.ca>; HC.F ORA_COVID / BAR_COVID F.SC <hc.ora_covid-bar_covid.sc@canada.ca>; Raymond, Joel (HC/SC) <joel.raymond@canada.ca>; Ali, Osman (HC/SC) <osman.ali@canada.ca>
Cc: Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>; Rose, Jhona (HC/SC) <jhona.rose@canada.ca>; Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>; Salem, Myriam (HC/SC) <myriam.salem@canada.ca>
Subject: RE: BRDD action required: Pfizer BioNtech vaccine Memo to BRDD Control number: 251813 and 253419

Hi Saj,

I don't think we need a meeting for this, the MHPD memo is very clear.

I suggest the following wording for the clarifax, however comments are welcome. I'm afraid I don't know what RSI means (in the 4th request).
I would give them one week to submit the Post-authorization change.

1. Please add acute facial paralysis Under section 8.2 Clinical Trial Adverse Reactions/Unsolicited Adverse Events/Serious Adverse Events

Through the clinical trial safety follow-up period to 14 November 2020, acute peripheral facial paralysis (or palsy) was reported by four participants in the COVID-19 mRNA Vaccine group. Onset was Day 37 after Dose 1 (participant did not receive Dose 2) and Days 3, 9, and 48 after Dose 2. No cases of acute peripheral facial paralysis (or palsy) were reported in the placebo group.

As frequency has not been assessed in Canada, the addition of these events as Unknown frequency is recommended:

2. The addition of facial paralysis/Bell's Palsy Under Post-Market Adverse Reactions

Nervous System Disorders: facial paralysis/Bell's Palsy

3. The addition of an Unknown frequency paragraph in the Patient Medication Information under:

What are possible side effects from using Pfizer-BioNTech COVID-19 Vaccine? Like all vaccines, Pfizer-BioNTech COVID-19 Vaccine can cause side effects.
Side effects may occur at the following frequencies:

Unknown:

Facial paralysis/Bell's Palsy

4. We also request that the MAH update the Canadian Product Monograph to align with the Company Data Sheet (CDS) including but not limited to the following events Asthenia, Lethargy, Decreased appetite, Hyperhidrosis, Night sweats, Paresthesia, tachycardia and hypoesthesia.

Thanks,

Gina

From: Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>

Sent: 2021-07-13 10:49 AM

To: Bouthillier, Leo (HC/SC) <leo.bouthillier@canada.ca>; Cherry, Elana (HC/SC) <elana.cherry@canada.ca>; Faraci, Maria (HC/SC) <maria.faraci@canada.ca>; Coleman, Gina (HC/SC) <gina.coleman@canada.ca>; HC.F ORA_COVID / BAR_COVID F.SC <hc.ora_covid-

bar_covid.sc@canada.ca; Raymond, Joel (HC/SC) <joel.raymond@canada.ca>; Ali, Osman (HC/SC) <osman.ali@canada.ca>

Cc: Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>; Rose, Jhona (HC/SC) <jhona.rose@canada.ca>; Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>; Salem, Myriam (HC/SC) <myriam.salem@canada.ca>

Subject: RE: BRDD action required: Pfizer BioNtech vaccine Memo to BRDD Control number: 251813 and 253419

Looping BRDD risk team in as well. Saj

From: Alhaddad, Saj (HC/SC)

Sent: 2021-07-13 10:47 AM

To: Bouthillier, Leo (HC/SC) <leo.bouthillier@canada.ca>; Cherry, Elana (HC/SC) <elana.cherry@canada.ca>; Faraci, Maria (HC/SC) <maria.faraci@canada.ca>; Coleman, Gina (HC/SC) <gina.coleman@canada.ca>; HC.F ORA_COVID / BAR_COVID F.SC <hc.ora_covid_bar_covid.sc@canada.ca>

Cc: Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>; Rose, Jhona (HC/SC) <jhona.rose@canada.ca>; Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>; Salem, Myriam (HC/SC) <myriam.salem@canada.ca>

Subject: BRDD action required: Pfizer BioNtech vaccine Memo to BRDD Control number: 251813 and 253419

Good morning BRDD team,

The MHPD created a memo based on the review of MSR#5 and MSR#6 on facial paralysis for the PFIZER-BIONTEH COVID-19 Vaccine: [HC6-024-e243022 \(1.0\) Reg Info - Post Market Tracker](#)

Please find actions in the memo for BRDD's immediate action. Should you require a meeting to discuss this, please let us know.

Regards,

Saj Alhaddad

A/ Senior Regulatory Project Manager - Gestionnaire principal de projets réglementaires par intérim

Bureau of Biologics, Radiopharmaceuticals and Self-Care Products | Bureau des produits biologiques, radiopharmaceutiques et de soins autoadministrés

Marketed Health Products Directorate - (MHPD) | Direction des produits de santé commercialisés - (DPSC)

Saj.alhaddad@canada.ca

Tel : (613) 240-9514

From: [Salem, Myriam \(HC/SC\)](#)
Sent: 2021-07-13 11:28 AM
To: [Coleman, Gina \(HC/SC\)](#)
Subject: RE: BRDD action required: Pfizer BioNtech vaccine Memo to BRDD Control number: 251813 and 253419

Thanks Gina,
 Have a good day,
 Myriam

From: Coleman, Gina (HC/SC) <gina.coleman@canada.ca>
Sent: 2021-07-13 11:13 AM
To: Salem, Myriam (HC/SC) <myriam.salem@canada.ca>
Subject: RE: BRDD action required: Pfizer BioNtech vaccine Memo to BRDD Control number: 251813 and 253419

Thank you Myriam!

From: Salem, Myriam (HC/SC) <myriam.salem@canada.ca>
Sent: 2021-07-13 11:12 AM
To: Coleman, Gina (HC/SC) <gina.coleman@canada.ca>; Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>; Bouthillier, Leo (HC/SC) <leo.bouthillier@canada.ca>; Cherry, Elana (HC/SC) <elana.cherry@canada.ca>; Faraci, Maria (HC/SC) <maria.faraci@canada.ca>; HC.F ORA_COVID / BAR_COVID F.SC <hc.ora_covid-bar_covid.sc@canada.ca>; Raymond, Joel (HC/SC) <joel.raymond@canada.ca>; Ali, Osman (HC/SC) <osman.ali@canada.ca>
Cc: Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>; Rose, Jhona (HC/SC) <jhona.rose@canada.ca>; Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>
Subject: RE: BRDD action required: Pfizer BioNtech vaccine Memo to BRDD Control number: 251813 and 253419

Hi Gina,

RSI is the Reference Safety Information; however, I have changed it below to CDS (Core Data Sheet) in red.

Thank you,
 Myriam

From: Coleman, Gina (HC/SC) <gina.coleman@canada.ca>
Sent: 2021-07-13 11:07 AM
To: Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>; Bouthillier, Leo (HC/SC) <leo.bouthillier@canada.ca>; Cherry, Elana (HC/SC) <elana.cherry@canada.ca>; Faraci, Maria (HC/SC) <maria.faraci@canada.ca>; HC.F ORA_COVID / BAR_COVID F.SC <hc.ora_covid-bar_covid.sc@canada.ca>

bar_covid.sc@canada.ca>; Raymond, Joel (HC/SC) <joel.raymond@canada.ca>; Ali, Osman (HC/SC) <osman.ali@canada.ca>

Cc: Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>; Rose, Jhona (HC/SC) <jhona.rose@canada.ca>; Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>; Salem, Myriam (HC/SC) <myriam.salem@canada.ca>

Subject: RE: BRDD action required: Pfizer BioNtech vaccine Memo to BRDD Control number: 251813 and 253419

Hi Saj,

I don't think we need a meeting for this, the MHPD memo is very clear.

I suggest the following wording for the clarifax, however comments are welcome. I'm afraid I don't know what RSI means (in the 4th request).

I would give them one week to submit the Post-authorization change.

1. Please add acute facial paralysis Under section 8.2 Clinical Trial Adverse Reactions/Unsolicited Adverse Events/Serious Adverse Events

Through the clinical trial safety follow-up period to 14 November 2020, acute peripheral facial paralysis (or palsy) was reported by four participants in the COVID-19 mRNA Vaccine group. Onset was Day 37 after Dose 1 (participant did not receive Dose 2) and Days 3, 9, and 48 after Dose 2. No cases of acute peripheral facial paralysis (or palsy) were reported in the placebo group.

As frequency has not been assessed in Canada, the addition of these events as Unknown frequency is recommended:

2. The addition of facial paralysis/Bell's Palsy Under Post-Market Adverse Reactions

Nervous System Disorders: facial paralysis/Bell's Palsy

3. The addition of an Unknown frequency paragraph in the Patient Medication Information under:

What are possible side effects from using Pfizer-BioNTech COVID-19 Vaccine? Like all vaccines, Pfizer-BioNTech COVID-19 Vaccine can cause side effects.

Side effects may occur at the following frequencies:

Unknown:

Facial paralysis/Bell's Palsy

4. We also request that the MAH update the Canadian Product Monograph to align with the Company Data Sheet (CDS) including but not limited to the following events Asthenia, Lethargy, Decreased appetite, Hyperhidrosis, Night sweats, Paresthesia, tachycardia and hypoesthesia.

Thanks,

Gina

From: Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>
Sent: 2021-07-13 10:49 AM
To: Bouthillier, Leo (HC/SC) <leo.bouthillier@canada.ca>; Cherry, Elana (HC/SC) <elana.cherry@canada.ca>; Faraci, Maria (HC/SC) <maria.faraci@canada.ca>; Coleman, Gina (HC/SC) <gina.coleman@canada.ca>; HC.F ORA_COVID / BAR_COVID F.SC <hc.ora_covid_bar_covid.sc@canada.ca>; Raymond, Joel (HC/SC) <joel.raymond@canada.ca>; Ali, Osman (HC/SC) <osman.ali@canada.ca>
Cc: Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>; Rose, Jhona (HC/SC) <jhona.rose@canada.ca>; Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>; Salem, Myriam (HC/SC) <myriam.salem@canada.ca>
Subject: RE: BRDD action required: Pfizer BioNtech vaccine Memo to BRDD Control number: 251813 and 253419

Looping BRDD risk team in as well. Saj

From: Alhaddad, Saj (HC/SC)
Sent: 2021-07-13 10:47 AM
To: Bouthillier, Leo (HC/SC) <leo.bouthillier@canada.ca>; Cherry, Elana (HC/SC) <elana.cherry@canada.ca>; Faraci, Maria (HC/SC) <maria.faraci@canada.ca>; Coleman, Gina (HC/SC) <gina.coleman@canada.ca>; HC.F ORA_COVID / BAR_COVID F.SC <hc.ora_covid_bar_covid.sc@canada.ca>
Cc: Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>; Rose, Jhona (HC/SC) <jhona.rose@canada.ca>; Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>; Salem, Myriam (HC/SC) <myriam.salem@canada.ca>
Subject: BRDD action required: Pfizer BioNtech vaccine Memo to BRDD Control number: 251813 and 253419

Good morning BRDD team,

The MHPD created a memo based on the review of MSR#5 and MSR#6 on facial paralysis for the PFIZER-BIONTEH COVID-19 Vaccine: [HC6-024-e243022 \(1.0\) Reg Info - Post Market Tracker](#)

Please find actions in the memo for BRDD's immediate action. Should you require a meeting to discuss this, please let us know.

Regards,

Saj Alhaddad

A/ Senior Regulatory Project Manager - Gestionnaire principal de projets réglementaires par intérim

Bureau of Biologics, Radiopharmaceuticals and Self-Care Products | Bureau des produits
biologiques, radiopharmaceutiques et de soins autoadministrés
Marketed Health Products Directorate - (MHPD) | Direction des produits de santé commercialisés -
(DPSC)

Saj.alhaddad@canada.ca

Tel : (613) 240-9514

From: [Hunt, Melissa \(HC/SC\)](#)
Sent: 2021-07-13 8:59 AM
To: [Salem, Myriam \(HC/SC\)](#); [Alhaddad, Saj \(HC/SC\)](#); [Rose, Jhona \(HC/SC\)](#)
Cc: [Stothart, Tonja \(HC/SC\)](#)
Subject: RE: For Director Review/Signature Pfizer BioNtech vaccine MSR6 and letter to MAH (DSTS#253419)

Signed ☺ Thanks all!

From: Salem, Myriam (HC/SC) <myriam.salem@canada.ca>
Sent: 2021-07-13 8:58 AM
To: Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>; Rose, Jhona (HC/SC) <jhona.rose@canada.ca>; Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>
Cc: Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>
Subject: RE: For Director Review/Signature Pfizer BioNtech vaccine MSR6 and letter to MAH (DSTS#253419)

Good morning all,

I removed the Moderna reference. The document should be ready.

Thanks,
 Myriam

From: Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>
Sent: 2021-07-13 8:40 AM
To: Rose, Jhona (HC/SC) <jhona.rose@canada.ca>; Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>; Salem, Myriam (HC/SC) <myriam.salem@canada.ca>
Cc: Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>
Subject: RE: For Director Review/Signature Pfizer BioNtech vaccine MSR6 and letter to MAH (DSTS#253419)

I agree with the classification and I also agree with Jhona, Myriam, this was a review of facial paralysis of Pfizer only correct? If so we should remove “moderna” from the subject line as Jhona suggested.
 Saj

From: Rose, Jhona (HC/SC) <jhona.rose@canada.ca>
Sent: 2021-07-13 8:27 AM
To: Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>; Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>; Salem, Myriam (HC/SC) <myriam.salem@canada.ca>
Cc: Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>

Subject: RE: For Director Review/Signature Pfizer BioNtech vaccine MSR6 and letter to MAH (DSTS#253419)

Good morning,

I just quickly check the memo. The subject line is for Pfizer and Moderna but the summary data only covered Pfizer. Moderna is not mentioned anywhere else in the document.

Thank you.

Jhona

From: Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>

Sent: 2021-07-13 7:54 AM

To: Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>; Salem, Myriam (HC/SC) <myriam.salem@canada.ca>

Cc: Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>; Rose, Jhona (HC/SC) <jhona.rose@canada.ca>

Subject: RE: For Director Review/Signature Pfizer BioNtech vaccine MSR6 and letter to MAH (DSTS#253419)

Thank you Saj,

I added "Protected B" as security classification (I think that is what it would be). If any disagree let me know shortly (I will sign around 9).

Thanks

Melissa

From: Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>

Sent: 2021-07-12 8:59 PM

To: Salem, Myriam (HC/SC) <myriam.salem@canada.ca>; Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>

Cc: Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>; Rose, Jhona (HC/SC) <jhona.rose@canada.ca>

Subject: RE: For Director Review/Signature Pfizer BioNtech vaccine MSR6 and letter to MAH (DSTS#253419)

Made some edits, added the control numbers for MSSR 5 and 6 for Pfizer and updated the metadata as well. Saj

From: Salem, Myriam (HC/SC) <myriam.salem@canada.ca>

Sent: 2021-07-12 4:25 PM

To: Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>; Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>

Cc: Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>; Rose, Jhona (HC/SC) <jhona.rose@canada.ca>

Subject: RE: For Director Review/Signature Pfizer BioNtech vaccine MSR6 and letter to MAH (DSTS#253419)

Yes should be available through this link:
[HC6-024-e243022 \(1.0\) Reg Info - Post Market Tracker](#)

Thank you,
 Myriam

From: Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>

Sent: 2021-07-12 4:18 PM

To: Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>; Salem, Myriam (HC/SC) <myriam.salem@canada.ca>

Cc: Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>; Rose, Jhona (HC/SC) <jhona.rose@canada.ca>

Subject: RE: For Director Review/Signature Pfizer BioNtech vaccine MSR6 and letter to MAH (DSTS#253419)

Ok- both signed.

Memo to BRDD will also be uploaded to DB, correct?

I'm ready to sign that as well.

Thanks
 Melissa

From: Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>

Sent: 2021-07-12 4:09 PM

To: Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>; Salem, Myriam (HC/SC) <myriam.salem@canada.ca>

Cc: Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>; Rose, Jhona (HC/SC) <jhona.rose@canada.ca>

Subject: RE: For Director Review/Signature Pfizer BioNtech vaccine MSR6 and letter to MAH (DSTS#253419)

The Letter is good. Saj

From: Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>

Sent: 2021-07-12 4:01 PM

To: Salem, Myriam (HC/SC) <myriam.salem@canada.ca>; Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>

Cc: Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>; Rose, Jhona (HC/SC)

<jhona.rose@canada.ca>

Subject: RE: For Director Review/Signature Pfizer BioNtech vaccine MSR6 and letter to MAH (DSTS#253419)

Hi Myriam,

Letter looks good. I added the new bits into the Review.

Last chance for verification of those docs and I will sign (**Saj- is letter OK to sign?**)

Then we can work to send the Memo to BRDD.

MERCI!

Melissa

From: Salem, Myriam (HC/SC) <myriam.salem@canada.ca>

Sent: 2021-07-12 2:26 PM

To: Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>; Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>

Cc: Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>; Rose, Jhona (HC/SC) <jhona.rose@canada.ca>

Subject: RE: For Director Review/Signature Pfizer BioNtech vaccine MSR6 and letter to MAH (DSTS#253419)

Hi Melissa,

Please note that the latest version of the letter is ready for your review,

Thank you,
Myriam

From: Salem, Myriam (HC/SC)

Sent: 2021-07-12 9:44 AM

To: Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>; Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>

Cc: Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>; Rose, Jhona (HC/SC) <jhona.rose@canada.ca>

Subject: RE: For Director Review/Signature Pfizer BioNtech vaccine MSR6 and letter to MAH (DSTS#253419)

Hi Melissa,

Thank you, I have updated/cleaned the MSR and letter on docuBridge and attached the memo for your review. I will upload the memo as soon as it is approved.

Thanks,
Myriam

From: Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>
Sent: 2021-07-12 6:48 AM
To: Salem, Myriam (HC/SC) <myriam.salem@canada.ca>; Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>
Cc: Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>; Rose, Jhona (HC/SC) <jhona.rose@canada.ca>
Subject: RE: For Director Review/Signature Pfizer BioNtech vaccine MSR6 and letter to MAH (DSTS#253419)

Hi Myriam,

I made minor comments in the Exec Summary and I tried to match the letter to the exec summary. Can you take a look? We're almost ready to go 😊

Then if these could be reflected in the BRDD memo that would be great.

Jhona- This is done and you don't need to do anything. 😊 Just FYI that in discussions with BRDD last week we decided that for any labelling updated we would consistently send a memo to BRDD to action (and then raise at our bilats to make sure on the radar). We did not do that for AZ last week (we put general recommendation in our letter following MSSR), but we checked with BRDD before that.

Thanks!
Melissa

From: Salem, Myriam (HC/SC) <myriam.salem@canada.ca>
Sent: 2021-07-09 4:32 PM
To: Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>; Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>
Cc: Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>
Subject: RE: For Director Review/Signature Pfizer BioNtech vaccine MSR6 and letter to MAH (DSTS#253419)

Thank you Melissa, I have updated the MSR, and addressed the comments. Will follow shortly with the memo for your review.

Merci beaucoup,
Myriam

From: Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>
Sent: 2021-07-09 3:30 PM
To: Salem, Myriam (HC/SC) <myriam.salem@canada.ca>; Alhaddad, Saj (HC/SC)

<saj.alhaddad@canada.ca>

Cc: Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>

Subject: RE: For Director Review/Signature Pfizer BioNtech vaccine MSR6 and letter to MAH (DSTS#253419)

Hi Myriam,

I have a few additional changes and comments in the docubridge version. Also invite Tonja if anything additional.

I think we will likely wrap this up on Monday morning. As discussed we'll need a memo to BRDD for the labelling changes too.

Thank you so very much!
Melissa

From: Salem, Myriam (HC/SC) <myriam.salem@canada.ca>

Sent: 2021-07-09 10:52 AM

To: Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>; Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>

Cc: Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>

Subject: RE: For Director Review/Signature Pfizer BioNtech vaccine MSR6 and letter to MAH (DSTS#253419)

Thank you Saj,

Please find below the corrected link:
[HC6-024-e243022 \(1.0\) Reg Info - Post Market Tracker](#)

Thanks,
Myriam

From: Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>

Sent: 2021-07-09 10:38 AM

To: Salem, Myriam (HC/SC) <myriam.salem@canada.ca>; Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>

Cc: Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>

Subject: RE: For Director Review/Signature Pfizer BioNtech vaccine MSR6 and letter to MAH (DSTS#253419)

Thank you for giving me access Myriam,
Both of these documents are identical, I think you accidentally dragged and dropped the same thing.

FYI the report is from April 30 to May 31 if we wish to make that edit on the cover page of the report.

I will add the control number as soon as you re-upload the letter to MAH.

Regards,

Saj

From: Salem, Myriam (HC/SC) <myriam.salem@canada.ca>

Sent: 2021-07-09 10:28 AM

To: Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>

Cc: Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>; Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>

Subject: For Director Review/Signature Pfizer BioNtech vaccine MSR6 and letter to MAH (DSTS#253419)

Hi Melissa,

Please note that the Summary Monthly Safety Report #6 and letter to MAH for Pfizer-BioNtech were uploaded to docuBridge for your review and signature.

[HC6-024-e243022 \(1.0\) Reg Info - Post Market Tracker](#)

[HC6-024-e243022 \(1.0\) Reg Info - Post Market Tracker](#)

The documents were also shared with Saj and Tonja.

Thank you,

Myriam

From: [Hunt, Melissa \(HC/SC\)](#)
Sent: 2021-06-17 9:28 AM
To: [Alhaddad, Saj \(HC/SC\)](#); [Rose, Jhona \(HC/SC\)](#); [Stothart, Tonja \(HC/SC\)](#)
Cc: [Bouthillier, Leo \(HC/SC\)](#); [Blahoianu, Maria \(HC/SC\)](#); [Salem, Myriam \(HC/SC\)](#); [HC.F ORA COVID / BAR COVID F.SC](#)
Subject: RE: Meeting to Discuss Product Monograph

Hi Saj,

Agree that our BRDD colleagues should be there!

11:30 works for me.

Thanks,
 Melissa

From: Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>
Sent: 2021-06-17 9:27 AM
To: Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>; Rose, Jhona (HC/SC) <jhona.rose@canada.ca>; Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>
Cc: Bouthillier, Leo (HC/SC) <leo.bouthillier@canada.ca>; Blahoianu, Maria (HC/SC) <maria.blahoianu@canada.ca>; Salem, Myriam (HC/SC) <myriam.salem@canada.ca>; HC.F ORA_COVID / BAR_COVID F.SC <hc.ora_covid-bar_covid.sc@canada.ca>
Subject: RE: Meeting to Discuss Product Monograph

Good morning Melissa,

As you already know; we asked for PM updates for facial paralysis/Bell's Palsy, Myocarditis/Pericarditis however in their latest MSSR submission response to our letter: [HC6-024-e243022 \(253419 - Response to MHPD Request dated 2021-06-07\) - Response to MHPD request of Jun-07-2021 \(PDF\)](#) they indicate that there are inconclusive evidence for such labeling, they will continue to evaluate and propose wording if warranted upon future assessments. They are also not proposing any changes with regards to thrombosis and thrombocytopenia to the PM nor the RMP among other safety updates. I believe that they want to discuss all these topics and their plans for what they plan to include and what won't be included in the next PM update.

Looping Leo and Maria in since it would be important to have them on the call with us.

Based on our schedules (Monday from 11:30 to 12:00 is free) please let me know if I can go ahead and coordinate with Pfizer.

Thank you,
 Saj

From: Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>
Sent: 2021-06-17 6:51 AM
To: Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>; Rose, Jhona (HC/SC) <jhona.rose@canada.ca>; Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>
Subject: RE: Meeting to Discuss Product Monograph

Thanks Saj,

Sounds good, I wonder if it has to do with alignment of the reference safety information...

Thanks,
Melissa

From: Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>
Sent: 2021-06-16 10:49 PM
To: Rose, Jhona (HC/SC) <jhona.rose@canada.ca>; Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>; Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>
Subject: FW: Meeting to Discuss Product Monograph

Hello,
Just an FYI, Pfizer would like to schedule a quick call to discuss upcoming revisions to their PM.
I will check your schedules and coordinate with BRDD.
Thank you,
Saj

From: [REDACTED] <[REDACTED]@Pfizer.com>
Sent: 2021-06-16 6:03 PM
To: Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>; Eassa, Samar (HC/SC) <samar.eassa@canada.ca>
Cc: [REDACTED] <[REDACTED]@pfizer.com>
Subject: Meeting to Discuss Product Monograph

Dear Samar & Saj,

As a follow-up to our pre-NDS meeting on 3 Jun and further to the response to the MHPDs request of 7 Jun 2021 (seq 0133 filed on 15 Jun 2021), we would like to request a short call with BRRD/MHPD to discuss upcoming revisions to the Product Monograph for COMIRNATY.

We would appreciate having the call early next week, 30 minutes would suffice, and we can be available anytime next Monday or Tuesday or between 8:30-noon on Wednesday.

Sincerely,

[REDACTED]

From: [Salem, Myriam \(HC/SC\)](#)
Sent: 2021-06-18 9:40 AM
To: [Rose, Jhona \(HC/SC\)](#)
Subject: RE: Meeting to Discuss Product Monograph

Thanks Jhona

From: Rose, Jhona (HC/SC) <jhona.rose@canada.ca>
Sent: 2021-06-18 9:11 AM
To: Salem, Myriam (HC/SC) <myriam.salem@canada.ca>
Subject: RE: Meeting to Discuss Product Monograph

Good idea. I can proposed that for sure.

From: Salem, Myriam (HC/SC) <myriam.salem@canada.ca>
Sent: 2021-06-18 9:09 AM
To: Rose, Jhona (HC/SC) <jhona.rose@canada.ca>
Subject: RE: Meeting to Discuss Product Monograph

Good morning Jhona,

Will there be an internal meeting before meeting with the company?

Thanks,
 Myriam

From: Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>
Sent: 2021-06-17 9:27 AM
To: Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>; Rose, Jhona (HC/SC) <jhona.rose@canada.ca>; Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>
Cc: Bouthillier, Leo (HC/SC) <leo.bouthillier@canada.ca>; Blahoianu, Maria (HC/SC) <maria.blahoianu@canada.ca>; Salem, Myriam (HC/SC) <myriam.salem@canada.ca>; HC.F
 ORA_COVID / BAR_COVID F.SC <hc.ora_covid-bar_covid.sc@canada.ca>
Subject: RE: Meeting to Discuss Product Monograph

Good morning Melissa,

As you already know; we asked for PM updates for facial paralysis/Bell's Palsy, Myocarditis/Pericarditis however in their latest MSSR submission response to our letter: [HC6-024-e243022 \(253419 - Response to MHPD Request dated 2021-06-07\) - Response to MHPD request of Jun-07-2021 \(PDF\)](#) they indicate that there are inconclusive evidence for such labeling, they will continue to evaluate and propose wording if warranted upon future assessments. They are also not proposing any changes with regards to thrombosis and thrombocytopenia to the PM nor the

RMP among other safety updates. I believe that they want to discuss all these topics and their plans for what they plan to include and what won't be included in the next PM update.

Looping Leo and Maria in since it would be important to have them on the call with us.

Based on our schedules (Monday from 11:30 to 12:00 is free) please let me know if I can go ahead and coordinate with Pfizer.

Thank you,
Saj

From: Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>
Sent: 2021-06-17 6:51 AM
To: Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>; Rose, Jhona (HC/SC) <jhona.rose@canada.ca>; Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>
Subject: RE: Meeting to Discuss Product Monograph

Thanks Saj,

Sounds good, I wonder if it has to do with alignment of the reference safety information...

Thanks,
Melissa

From: Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>
Sent: 2021-06-16 10:49 PM
To: Rose, Jhona (HC/SC) <jhona.rose@canada.ca>; Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>; Stothart, Tonja (HC/SC) <tonja.stothart@canada.ca>
Subject: FW: Meeting to Discuss Product Monograph

Hello,
Just an FYI, Pfizer would like to schedule a quick call to discuss upcoming revisions to their PM. I will check your schedules and coordinate with BRDD.
Thank you,
Saj

From: [REDACTED] <[REDACTED]@Pfizer.com>
Sent: 2021-06-16 6:03 PM
To: Alhaddad, Saj (HC/SC) <saj.alhaddad@canada.ca>; Eassa, Samar (HC/SC) <samar.eassa@canada.ca>
Cc: [REDACTED] <[REDACTED]@pfizer.com>
Subject: Meeting to Discuss Product Monograph

Dear Samar & Saj,

As a follow-up to our pre-NDS meeting on 3 Jun and further to the response to the MHPDs request of 7 Jun 2021 (seq 0133 filed on 15 Jun 2021), we would like to request a short call with BRRD/MHPD to discuss

upcoming revisions to the Product Monograph for COMIRNATY.

We would appreciate having the call early next week, 30 minutes would suffice, and we can be available anytime next Monday or Tuesday or between 8:30-noon on Wednesday.

Sincerely,

A black rectangular redaction box covering the signature.

From: [Alhaddad, Saj \(HC/SC\)](#)
Sent: 2021-07-13 10:54 AM
To: [HC.F BBRS COVID Vaccines Team / Equipe Vaccins COVID du BBRA F.SC](#); [Major, Karen \(HC/SC\)](#); [Chen, Stella \(HC/SC\)](#)
Cc: [Bouthillier, Leo \(HC/SC\)](#); [Cherry, Elana \(HC/SC\)](#); [Blahoianu, Maria \(HC/SC\)](#); [HC.F ORA COVID / BAR COVID F.SC](#)
Subject: RE: MHPD completed COVID vaccine reviews: RMP updates and Monthly Safety Reviews

Hi team,

The Pfizer-BioNTech COVID-19 Vaccine MSSR#6 (control #253419) has been reviewed:

Review report: [HC6-024-e243022 \(1.0\) Reg Info - Post Market Tracker](#)

Letters to the sponsor: [HC6-024-e243022 \(1.0\) Reg Info - Post Market Tracker](#)

Memo to BRDD with MHPD recommending a labeling change on facial paralysis: [HC6-024-e243022 \(1.0\) Reg Info - Post Market Tracker](#)

FYI, BRDD

Thank you,

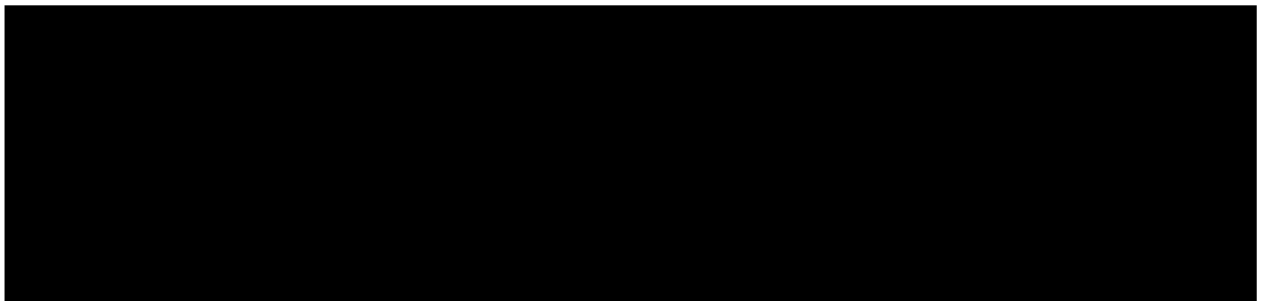
Saj

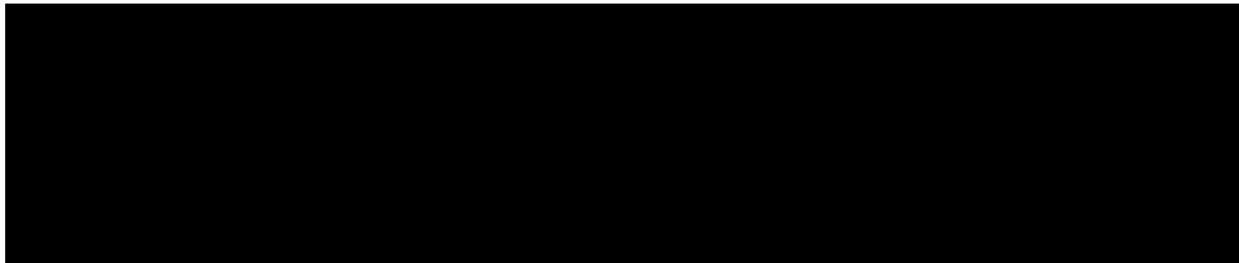
From: Alhaddad, Saj (HC/SC)
Sent: 2021-07-08 2:09 PM
To: HC.F BBRS COVID Vaccines Team / Equipe Vaccins COVID du BBRA F.SC
[<hc.bbrcovidvaccinesteam-equipevaccinscoviddubbra.sc@canada.ca>](mailto:hc.bbrcovidvaccinesteam-equipevaccinscoviddubbra.sc@canada.ca)
Cc: Bouthillier, Leo (HC/SC) [<leo.bouthillier@canada.ca>](mailto:leo.bouthillier@canada.ca); Cherry, Elana (HC/SC) [<elana.cherry@canada.ca>](mailto:elana.cherry@canada.ca); Blahoianu, Maria (HC/SC) [<maria.blahoianu@canada.ca>](mailto:maria.blahoianu@canada.ca); HC.F ORA_COVID / BAR_COVID F.SC [<hc.ora_covid-bar_covid.sc@canada.ca>](mailto:hc.ora_covid-bar_covid.sc@canada.ca)
Subject: MHPD completed COVID vaccine reviews: RMP updates and Monthly Safety Reviews

Hi team,

With **HUGE** thanks to everyone involved, the BBRS-CRT team completed the following reviews and issued a number of decision letters to the approved COVID-19 vaccines below:

Review of Monthly Safety Reviews completed:

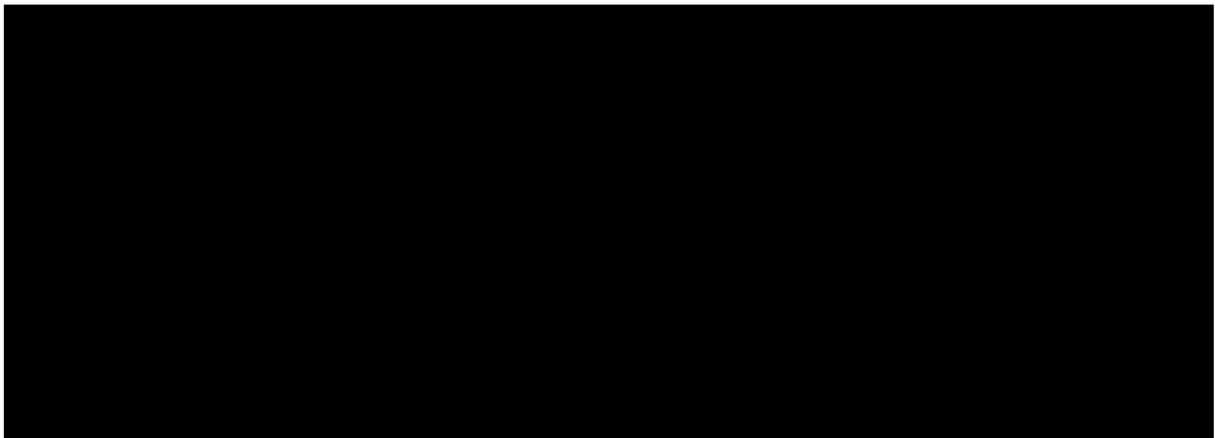




*We are in the final stages of the review of the Pfizer-BioNTech COVID-19 Vaccine latest monthly safety report #6, we expect to issue our decision tomorrow.

Review of updated RMPs completed:

- Pfizer-BioNTech COVID-19 Vaccine updated RMP (control #253040) – Review report: HC6-024-e243022 (1.0) Reg Info - Post Market Tracker Letter to the sponsor: HC6-024-e243022 (1.0) Reg Info - Post Market Tracker



The tracking sheets will be updated accordingly.

FYI, BRDD

Regards,

Saj Alhaddad

A/ Senior Regulatory Project Manager - Gestionnaire principal de projets réglementaires par intérim

Bureau of Biologics, Radiopharmaceuticals and Self-Care Products | Bureau des produits biologiques, radiopharmaceutiques et de soins autoadministrés

Marketed Health Products Directorate - (MHPD) | Direction des produits de santé commercialisés - (DPSC)

Saj.alhaddad@canada.ca

Tel : (613) 240-9514



**Health
Canada**

Health Products
and Food Branch

**Santé
Canada**

Direction générale des produits
de santé et des aliments

Marketed Health Products Directorate
Address Locator # 1906A
OTTAWA, Ontario
K1A 0K9

Date: June 30, 2021

Control #: 253040

[REDACTED]
[REDACTED] Regulatory Affairs
Pfizer Canada ULC
17300 Trans-Canada Highway
Kirkland, Quebec, Canada H9J 2M5
Fax: 514-426-6824

Dear [REDACTED]

**Re: Health Canada Review of the European Risk Management Plan V2.0
and Canadian Addendum for Pfizer-BioNTech COVID-19 Vaccine
(COVID-19 mRNA Vaccine)
(dated April 29, 2021 and May 2021)**

As part of Health Canada's efforts to minimize health risk factors to Canadians while maximizing the safety provided by the regulatory system for health products, the Marketed Health Products Directorate (MHPD) has completed a review of the European Risk Management Plan (RMP) Version 2.0, dated **April 29, 2021** in conjunction with the Canadian Addendum for **Pfizer-BioNTech COVID-19 Vaccine® (COVID-19 mRNA Vaccine)** dated **May 27, 2021**. Please find below actions for Pfizer Canada ULC stemming from this review.

According to the Terms and Conditions for the Risk Management Plan (RMP) item #14, Pfizer Canada ULC, is required to provide and update to the Canadian Addendum to include the following revisions:

To the Safety Specification Section

1. Addition of the following as **Important potential risk**:

a. Depression exacerbation in the pediatric population

An imbalance in reported serious adverse events in the vaccine arm compared to the placebo arm in pediatric Study 2 were observed. In addition, cases of depression and/or suicide were reported from post-market data. Based on this information, it is recommended that depression exacerbation in the pediatric population should be included in the RMP as an Important Potential Risk.

b. Myocarditis/Pericarditis

In light of the emerging data from international partners (including Israel and the United

States), cases in the literature and cases reported in Canada, demonstrating a possible association with myocarditis/pericarditis and the use of mRNA vaccines including Pfizer BioNTech COVID-19 Vaccine, it is recommend that” myocarditis and/or pericarditis” be included as an important potential risk.

2. Replace the following as **missing information**:

- a. “Interaction with other vaccine” should be replace by “**Interaction with other vaccine or other drug products**”. Interaction with other drug products including CYP 1A2 inhibitors, such as clozapine, has been observed in the post-market setting. The monthly safety report also included other potential interaction with other drug products.

To the Pharmacovigilance Plan

1. Update the Pharmacovigilance and risk minimization plan accordingly from the above additions to the safety specification.

A control number has been assigned for your submission of an updated Canadian Addendum in response to this letter. The control number is **254230**. Please provide the updated Canadian addendum before or on **July 12, 2021** and include this control number in the cover letter of your response, along with a copy of this letter.

Sponsors must now submit their regulatory transactions using the Regulatory Enrolment Process (REP). By using this process, transactions in both eCTD and non-eCTD formats can be securely submitted via the Common Electronic Submissions Gateway (CESG).

Questions concerning this request should be directed to Saj Alhaddad, Acting Senior Regulatory Project Manager, BBRS, MHPD, by email at hc.mbbnhpb.rpmgpr.bpbsnc.sc@canada.ca.

Thank you in advance for your cooperation.

Melissa Hunt
Director
Marketed Health Products Directorate

This document has been signed electronically using the Health Canada docuBridge system. /
Ce document a été signé électroniquement à l'aide du système docuBridge de Santé Canada.

From: Rose, Jhona (HC/SC)
Sent: 2021-07-06 10:14 PM
To: Salem, Myriam (HC/SC)
Subject: RE: Myocarditis_AdHoc_2021-06-27_0.3 (Biological plausibility incomplete).docx
Attachments: Myocarditis_AdHoc_2021-06-27_0.3 (Biological plausibility incomplete).docx

Follow Up Flag: Follow up
Flag Status: Flagged

Hello Myriam,
Please see attached with some comments/suggestions.
Most of it were adjustments to capture that this review is to formalized the regulatory changes that were already been done. Also, added some info from TTS-hoc on COVID-19 disease but it needs to be updated.

Thank you.
Jhona

From: Salem, Myriam (HC/SC) <myriam.salem@canada.ca>
Sent: 2021-06-28 12:22 AM
To: Rose, Jhona (HC/SC) <jhona.rose@canada.ca>
Subject: Myocarditis_AdHoc_2021-06-27_0.3 (Biological plausibility incomplete).docx

Hi Jhona,

Please find attached the Ad-Hoc review, I am still working on a short paragraph regarding the biological plausibility and will be sending it to you tomorrow. In the meantime, if you have any comments on the other sections, please let me know.

Thanks,
Myriam

Marketed Health Products Directorate
Direction des produits de santé commercialisés

Ad-Hoc Report

messenger ribonucleic acid (mRNA) COVID-19 Vaccines

Pfizer-BioNTech COVID-19 Vaccine and COVID-19 Vaccine Moderna

Myocarditis/Pericarditis

Control #???

Position Title: Director / Directeur(ice)
Bureau: Bureau of Biologics, Radiopharmaceuticals and Self-Care Products/ Bureau des produits biologiques, radiopharmaceutiques et auto-administratifs
Date: <Enter date of completion>
Signature: <i>This document has been signed electronically using the Health Canada docuBridge system.</i> / Ce document a été signé électroniquement à l'aide du système docuBridge de Santé Canada
Security – Classification – de sécurité: Protected B when completed / protégé B une fois terminé

Inclusion of confidential information (i.e., shared by another regulatory agency) into the assessment should be clearly identified (highlighted) and should be included if considered necessary.

MHPD – PROTECTED B

REVIEW REPORT

Title: Review Report: Drug name (generic name followed by trade name® in brackets) and adverse event

Date:

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DRAFT

MHPD – PROTECTED B

REVIEW REPORT

1. Issue:

mRNA vaccines have been authorized in Canada under a ministerial Interim Order in December 2020. There are currently two (2) mRNA vaccines authorized for use in Canada. The Pfizer-BioNTech COVID-19 Vaccine, also known as BNT and the Moderna Covid-19 Vaccine. Both vaccines are indicated for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). On May 05th the Pfizer vaccine received authorization to expand the indication to adolescents 12 to 15 years of age.

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In February 2021, The signal of myocarditis was first detected when the Israel Ministry of Health noted a cluster of myocarditis cases following the mRNA Pfizer Covid-19 vaccine in February 2021. Following this media feed Following the review of monthly safety update report for February 2021, no new signal was identified; however, Health Canada requested more information on cardiac issues such as Cardiac Failure, and Myocardial infarction.

Commented [JR1]:

In March 2021, Cases of myocarditis following vaccination with Pfizer BioNTech COVID-19 Vaccine was first discussed at the international regulatory meeting, Pharmacovigilance Cluster, on March 3, 2021. The European Medicines Agency (EMA) discussed the information they received from the Israeli Ministry of Health regarding their investigation on a safety signal of myocarditis/pericarditis in younger population (16-30 years of age) following vaccination with Pfizer-BioNTech COVID-19 Vaccine (see Appendix I). At the time, the Israeli Ministry of Health have received 40 cases appearing adjacent to the administration of the vaccine. All regulatory members including the EMA, the U.S. Food Drugs Administration (FDA), European Medicines Agency (EMA), Medicines and Healthcare product Regulatory Agency (MHRA), Japan Pharmaceuticals and Medical Devices Agency (PMDA) and Health Canada were all in agreement that discussed myocarditis at the Pharmacovigilance Cluster teleconference. It was agreed at that time that myocarditis/pericarditis is not yet a safety signal and will continue to be monitored closely. there was no safety signal and standard post-market monitoring would continue for this issue. In the Monthly Safety Update Report #3 for March 2021 submitted to Health Canada, Pfizer noted a total of 72 myocarditis case reports since marketing and indicated that the observed rate of myocarditis did not exceed the expected rate in a general population (4.40 cases per 100,000 people/year). The report did not identify myocarditis as a validated safety signal. Health Canada reached out to Pfizer as well as the Ministry of Health in Israel for more information on the myocarditis reports in that jurisdiction. Pfizer did not consider the available evidence would support a safety signal, but confirmed the company will continue to monitor this issue.

Commented [JR2]: This should fit in the assessment section.

Following this meeting, myocarditis/pericarditis continued to be discussed at different international regulatory meetings including the ACCESS and ICMRA meeting for COVID-19 Vaccine. In addition,

Commented [JR3]:

MHPD – PROTECTED B**REVIEW REPORT**

On April 19, 2021, at the request of the MHRA, the MAH re-opened the signal to determine if myocarditis or pericarditis is a risk following vaccination of Pfizer BioNtech.

Commented [JR4]: Put this under MAH.

On May 15, 2021, Pfizer provided a cumulative review of Myocarditis and Pericarditis in the Monthly Summary Safety Report #5 for April 2021. The database was searched for spontaneous adverse events reports for Pfizer/BNT COVID-19 vaccine up to 17 April 2021. Pfizer identified 39 cases categorized as having some degree of certainty in diagnosis of myocarditis (definite, probable and possible cases). Pfizer concluded that there is no causal association based on the observed vs expected rates of myocarditis, pericarditis, clinical trial experience and post-authorization reports and closed the signal. The MHPD did not agree with this assessment. The MHPD requested a discussion on the risk mitigation strategies to be implemented in Canada, including PM safety update and recommended this issue be monitored separately from the monthly safety reports.

Commented [JR5]: MAH section

2. Purpose:

The goal of this adHocThe purpose of this review is to formalize the assessment on the risk of myocarditis/pericarditis events with the mRNA Vaccine (Pfizer-BioNTech COVID-19 Vaccine and COVID-19 Vaccine Moderna), to summarize the regulatory actions taken thus far, and to report is to continue monitoring and assessing emerging information on myocarditis with the mRNA vaccines in Canada and to determine the need for implementation of additional regulatory stepsrisk mitigation measures.

3. Background:

3.1 Product classification and Indications in Canada

3.1.1 Canada

There are currently two (2) COVID-19 mRNA Vaccines authorized in Canada:

- 1) PFIZER-BIONTECH COVID-19 VACCINE; First authorized under IO on December 9, 2020 for, also referred to as BNT162, is indicated for an active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS- CoV-2) in individuals 18 years of age and older. On May 5, 2021, this authorization was expanded to individuals age 12 years of age and older to 15.
- 2) COVID-19 Vaccine Moderna: Authorized under IO on December 23, 2020 for indicated for Aactive immunization against coronavirus disease 2019 (COVID-19) caused by the SARS-CoV-2 virus in individuals 18 years of age and older. The pediatric indication for individual age 12 to 15 is under review and expected to be authorized on July 8, 2021.

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3.1.1 Most of the evidence in this review report relates to the Pfizer-BioNtech vaccine; however, evidence related to Covid-19 vaccine Moderna is also being considered. As of June 23, 2021, the Pfizer BioNtech vaccine is the only Covid vaccine authorized for use in adolescents 12 to 17 years of age.

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Commented [JR6]: Not sure this fits here.

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REVIEW REPORT

The independent vaccine advisory committee in Canada, NACI, gave its approval on

Commented [JR7]:

International indications

3.1.2 European Medicines Agency

In the European Union, both mRNA vaccines: Pfizer-BioNTech (referred to as *Comirnaty*¹) and Moderna (referred to as *Spikevax*²) vaccines are indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus in adult patients but similar to Canada only the Pfizer-BioNTech vaccine is authorized in individuals 12 years of age and older. Spikevax is indicated in individuals 18 years of age and older.

Differences across EU member states exist when it comes to the use of the vaccine in the children/adolescents population. According to official recommendations stemming from independent member states vaccines committees, some members have limited the use in this patient population as illustrated by the examples below:

The Netherlands

On June 9, 2021, the Dutch Health Council gave a positive recommendation to begin vaccinating children aged 12 to 15³ who are vulnerable to serious symptoms of the coronavirus disease in addition to those aged 16 and 17 from high-risk groups⁴.

Germany

On June 10, 2021, the German vaccine advisory committee, the Standing Committee on vaccination (STIKO), gave limited approval for the pediatric indication given the lack of data on long-term effects. As reported by Reuters⁵, the panel said *it was not currently recommending the use of the vaccine for those aged 12-17 without pre-existing conditions, although noted doctors were allowed to give the shot if the individual accepts the risk.*

United Kingdom (UK)

On June 16, 2021, news reports⁶ suggested that the Joint Committee on Vaccination and Immunisation (JCVI) will not advise the Government to press ahead with a vaccination campaign for under-18s.

Commented [JR8]:

¹ https://www.ema.europa.eu/en/documents/product-information/comirnaty-epar-product-information_en.pdf

² <https://www.ema.europa.eu/en/medicines/human/EPAR/spikevax-previously-covid-19-vaccine-moderna>

³ [Netherlands-will-give-covid-vaccines-medically-vulnerable-adolescents](#)

⁴ [Covid-vaccination-starts-16-18-year-olds-high-risk-groups](#)

⁵ [German-panel-gives-limited-approval-covid-19-shot-adolescents](#)

⁶ [JCVI-not-recommending-vaccinating-children](#)

⁷ [Vaccination-experts-are-not-recommending-covid-jabs-for-under-18s-says-cabinet-minister](#)

MHPD – PROTECTED B

REVIEW REPORT

3.1.3 Food and Drug Administration

In the United States, both the Pfizer-BioNTech and Moderna mRNA vaccines were granted an Emergency Use Authorization (EUA) to permit the emergency use of these unapproved products, Pfizer-BioNTech COVID-19 Vaccine, and for active immunization to prevent COVID-19 in individuals 18 years of age and older. Similar to Canada, the Pfizer-BioNTech vaccine was authorized for use in individuals 12 years of age and older on May 10, 2021.

3.1.4 Israel

In Israel, the Pfizer-BioNTech vaccine is the only vaccine authorized for use in individuals 12 years of age and older.

3.1.5 MHRA**3.1.6 TGA****3.2 Product characteristics**

The nucleoside-modified messenger ribonucleic acid (mRNA) in the Pfizer-BioNTech COVID-19 Vaccine is formulated in lipid nanoparticles, which enable delivery of the non-replicating mRNA into the host's cells to allow expression of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike antigen⁸. The mRNA codes for membrane-anchored, full-length S with two point mutations within the central helix. Mutation of these two amino acids to proline locks S in an antigenically preferred prefusion conformation⁹. The protection against COVID-19 disease may be attributed to both the neutralizing antibody and immune cellular responses to the spike antigen¹⁰.

Both vaccines require a series of two (2) doses to complete vaccination administered 21 days apart (Pfizer) and 28 days apart (Moderna).

3.3 Product utilization??

Provide the estimated doses administered in Canada for both mRNA vaccines and other international regulatory agencies if available

⁸ Summary Basis of Decision - Pfizer-BioNTech COVID-19 Vaccine - Health Canada

⁹ Product-information/comirnaty-epar-product-information

¹⁰ Product Monograph Pfizer-BioNTech COVID-19 Vaccine dated May 19, 2021

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4. Relevant information of COVID-19 disease related to the indication

4.1 COVID-19 Disease

The coronavirus disease 2019 is the infectious disease caused by the recently discovered severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus that emerged in late 2019. In Canada, there have been 942,585 confirmed cases of COVID-19 and 22,716 deaths as of 21 March 2021.¹¹ It is predominantly a respiratory illness that can affect other organs. People with COVID-19 can be asymptomatic, or can experience a range of symptoms from mild to severe illness. Symptoms may appear 1 to 14 days after exposure to the virus, and may include fever or chills, cough, shortness of breath, fatigue, muscle or body aches, headache, loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, and diarrhea. The majority of patients infected with the SARS-CoV-2 virus recover without significant sequelae. However, 10% to 15% of cases progress to severe disease, and 5% of patients become critically ill. Significant risk factors such as age and underlying medical issues increase the likelihood of developing a severe disease. In around 30% of cases, symptoms may linger or recur over the weeks following the initial recovery, even in patients who had a mild disease.¹²

4.2 Treatment options for the indication

Care for individuals who have COVID-19 has improved with clinical experience, and clinical management of COVID-19 with a variety of therapies has continued to improve. To date, Health Canada has authorized three other vaccines under the Interim Order.

- On 9 December, 2020, the Pfizer-BioNTech COVID-19 Vaccine was authorized for active immunization to prevent COVID-19 caused by the SARS-CoV-2 virus in individuals 16 years of age and older.¹³
- On 23 December, 2020, the Moderna COVID-19 Vaccine was authorized for active immunization against COVID-19 caused by the SARS-CoV-2 virus in individuals 18 years of age and older.¹⁴

¹¹ <https://news.google.com/covid19/map?hl=en-CA&mid=%2Fm%2F0d060g&gl=CA&ceid=CA%3Aen>

¹² <https://covid-vaccine.canada.ca/info/summary-basis-decision-detailTwo.html?linkID=SBD00519>

¹³ <https://covid-vaccine.canada.ca/pfizer-biontech-covid-19-vaccine/product-details>

¹⁴ <https://covid-vaccine.canada.ca/covid-19-vaccine-moderna/product-details>

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Commented [JR9]:

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MHPD – PROTECTED B**REVIEW REPORT**

- On 26 February 2021, the AstraZeneca COVID-19 Vaccine and COVISHIELD were authorized for active immunization of individuals 18 years of age and over for the prevention of coronavirus disease 2019 (COVID-19).¹⁵
- On 5 March 2021, the Janssen COVID-19 Vaccine was authorized for active immunization for the prevention of coronavirus disease-2019 (COVID-19) caused by SARS-CoV-2 virus in individuals 18 years of age and older.¹⁶

In the context of the ongoing and worsening pandemic, an urgent need for further prophylactic vaccine options remains.

Mechanism of action

The nucleoside-modified messenger ribonucleic acid (mRNA) in the Pfizer-BioNTech COVID-19 Vaccine is formulated in lipid nanoparticles, which enable delivery of the non-replicating mRNA into the host's cells to allow expression of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike antigen¹⁷. The mRNA codes for membrane-anchored, full-length S with two point mutations within the central helix. Mutation of these two amino acids to proline locks S in an antigenically preferred prefusion conformation¹⁸. The protection against COVID-19 disease may be attributed to both the neutralizing antibody and immune cellular responses to the spike antigen¹⁹.

Both vaccines require a series of two (2) doses to complete vaccination administered 21 days apart (Pfizer) and 28 days apart (Moderna).

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4.5. Adverse event (s)***4.5.1 Description of the Adverse Event***

Myocarditis is an inflammatory disease of cardiac muscle that is caused by a variety of infectious and noninfectious conditions in adults²⁰. The incidence of myocarditis in children (below 15 years of age) is estimated at 1 to 2 per 100,000 children (Finland study). The true incidence of

¹⁵ <https://www.canada.ca/en/health-canada/services/drugs-health-products/covid19-industry/drugs-vaccines-treatments/vaccines/astrazeneca.html>

¹⁶ <https://covid-vaccine.canada.ca/janssen-covid-19-vaccine/product-details>

¹⁷ Summary Basis of Decision – Pfizer-BioNTech COVID-19 Vaccine – Health Canada

¹⁸ Product information/comirnaty epar product information

¹⁹ Product Monograph Pfizer-BioNTech COVID-19 Vaccine dated May 19, 2021

²⁰ Clinical manifestations and diagnosis of myocarditis in adults

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myocarditis is unknown and varies by season, age, and geography²¹. Peaks in infancy and adolescents have been reported in the medical literature; and a recent study reported 2.16 cases per 100,000 US military service members in a 30-day period. Clinical manifestations include a broad spectrum of signs including non-specific symptoms such as respiratory distress, and exhaustion. In severe cases, myocarditis may lead to cardiogenic shock and sudden death.

Myocarditis following mRNA vaccination has yet to be fully characterized; however, the spectrum of clinical manifestations appear to be less severe with most patients responding well to treatment and recovering quickly²².

4.25.2 Biological Plausibility

The mechanism of myocarditis/pericarditis following mRNA COVID vaccination is not well known at this time~~unknown~~. There are numerous proposed mechanisms that include:

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5.6. Issue Analysis

5.16.1 Regulatory assessments and/or Actions in Canada and internationally including vaccines committee recommendations

5.1.16.1.1 Current Product Monograph (PM) Labelling and International Labelling

5.1.1.16.1.1.1 Health Canada

Myocarditis and pericarditis are not currently captured in the Canadian Product Monograph. There is no labelling for 'myocarditis', 'myopericarditis', pericarditis or related myocarditis laboratory findings (elevation of troponin levels) in the current CPM (dated May 19, 2021) for the Pfizer-BioNTech COVID-19 Vaccine (CPM date???) and COVID-19 Vaccine Moderna (CPM date???) or any other currently COVID-19 vaccine in Canada including the mRNA vaccine from Moderna.

Following the Advisory Committee on Immunization Practices (ACIP) on June 23-25, 2021, Health Canada was informed via confidential agreement that the US Prescribing Information (USPI) for Pfizer-BioNTech COVID-19 Vaccine will be updated to reflect the risk of

²¹ Marshall M, Ferguson ID, Lewis P, et al. Symptomatic acute myocarditis in seven adolescents following Pfizer-BioNTech COVID-19 vaccination. *Pediatrics*. 2021; doi: 10.1542/peds.2021-052478 (Case report)

²² <https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/myocarditis.html>

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myocarditis and pericarditis following vaccination with this vaccine. On June 25, a courtesy copy of the draft USPI was shared by the FDA to Health Canada (see Appendix 2). Similarly on the same day, the MHRA updated their labelling for COVID-19 Vaccine Moderna on myocarditis and pericarditis.

On June 25, 2021, Health Canada issued an advisement letter to both MAHs (Pfizer Inc; ModernaTX Inc) to include the risk of myocarditis and pericarditis following vaccination with Pfizer-BioNTech COVID-19 Vaccine/Moderna. These CPMs are now updated (link for both PM).

6.1.1.2 European Medicines Agency (EMA)

In the EU, similar to Canada, there is no labelling for ‘myocarditis’ for any of the COVID-19 approved vaccines. Of note, the PRAC adopted a recommendation to initiate a signal assessment on this issue. Recommendations stemming from this review will be shared during the next PRAC meeting currently scheduled on July 24, 2021

6.1.1.3 Food and Drugs Administration

In the US, similar to Canada, there is no current labelling for ‘myocarditis’ for any of the COVID-19 approved vaccines.

6.1.1.4 Other regulatory agencies

There is no labeling for myocarditis in the Australian Therapeutic Goods Administration (TGA) label for the Pfizer Biontech vaccine, in the MedSafe New Zealand Data Sheet, the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) Drug Information sheet or the Israel information sheet.



²³ As of June 22, 2021

²⁴ Health Product InfoWatch – June 2021 - Canada.ca

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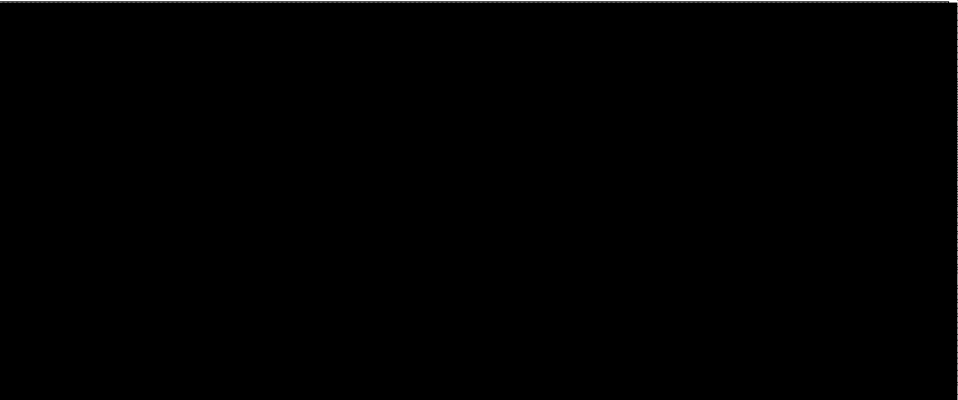
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6.1.2 Analysis of Adverse Events in Canada and Internationally

6.1.2.1 Cases reported during the clinical development

There were no case of myocarditis occurring after the Pfizer BioNTech mRNA vaccine and COVID-19 Moderna vaccines in the trials at time of authorization^{27,28}.

As reported by Pfizer in the monthly safety report #5²⁹ during the blinded placebo-controlled follow-up period, from study C4591001 (data-lock Mar 31, 2021) there was one report of myocarditis in the placebo group, and one report of pericarditis in the BNT162b2 group (a 66 year old white male who had pericarditis 29 days after dose 2 of vaccine which was ongoing at the time of the data cut-off. The case was assessed as not related to study intervention by the investigator).

6.1.2.2 Cases reported in the Pfizer BioNTech Monthly Safety Reports

In the Monthly Safety report #5 (DSTS# 251813, Review report: HC6-024-e243022 (1.0) Reg Info - Post Market Tracker) included a cumulative review of Pfizer assessed the cases of myocarditis and pericarditis? (up to April, 29, 2021).

²⁵ <https://www.gov.uk/government/publications/regulatory-approval-of-pfizer-biontech-vaccine-for-covid-19/information-for-healthcare-professionals-on-pfizerbiontech-covid-19-vaccine>

²⁶ <https://www.gov.uk/government/publications/regulatory-approval-of-covid-19-vaccine-moderna/information-for-healthcare-professionals-on-covid-19-vaccine-moderna>

²⁷ Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, Diemert D, Spector SA, Rouphael N, Creech CB, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. N Engl J Med. 2021;384:403-416.

²⁸ 2. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, Perez JL, Pérez Marc G, Moreira ED, Zerbini C, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med. 2020-Dec 31;383:2603-2615

²⁹ HC6-024-e243022 (251813 - For Period of 2021-04-01 to 2021-04-29) - Summary Monthly Safety Report (SMSR) 5 01-Apr-2021 through 29-Apr-2021) :

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Pfizer retrieved 278 reports of myocarditis and/or pericarditis and eliminated the ones that:

- did not contain enough clinical detail;
- described pericardial effusion without pericarditis or myocarditis;
- described pericardial effusion attributed to other diseases
- did not contain information describing pericarditis or myocarditis
- had an alternative explanations for pericarditis or myocarditis (including current COVID-19, history of autoimmune condition, renal failure, histories of tuberculosis).

The MAH analyzed the remaining 216 cases. From the analysis of the 216 cases, a pattern emerges from the time to vaccination to the emergence of myocarditis and/or pericarditis. The majority of cases were reported from the same day of vaccination up to 7 days following vaccination. The vast majority (95%, 11/216) of the cases were reported within 3 weeks of vaccination. However, some cases were reported up to 41 days following vaccination.

Out of the 216 patients, 67 patients had either recovered, had recovered with sequelae or were recovering, 39 had not recovered and 3 deaths were reported.

Of the initial 216 cases, 92 cases described events of pericarditis including one fatality in a 72 year old woman. 42/92 (46 %) were reported in female patients and 49/92 (53%) were reported in male patients. Half of the cases of pericarditis occurred following the first dose.

Of the initial 216 cases, 108 cases described events of myocarditis and 16 cases reported events of both Pericarditis and Myocarditis for a total of 124 cases reporting an event of myocarditis including 3 fatalities (a 19 year old male patient, a 49 year old male patient and an 81 year old woman). The vast majority of the myocarditis cases were reported in male patients. Furthermore, the majority of the myocarditis cases were reported following the second dose.

The MAH further assessed the 108 cases of myocarditis based on a recent publication by Bonaca et al defining an approach to the diagnosis of myocarditis. When applying Bonaca's definitions, the MAH found 8 definite cases of myocarditis, 10 probable cases and 21 possible cases for a total of 39 cases out of 124 cases being categorized as having some degree of certainty in diagnosis of myocarditis.

In the Monthly Safety report #6 (DSTS# 253419)³⁰, Pfizer retrieved 495 reports of myocarditis and pericarditis (up to May 25, 2021). Of the 495, there were 260 cases of myocarditis (all assessed as serious), 73 met a certainty in diagnosis of myocarditis when assessed based on the Brighton's Collaboration (BC) diagnostic certainty criteria. 18 cases Eighteen (18) cases were

³⁰ HC6-024-e243022 (253419 - Response to MHPD Request dated 2021-06-07) - Summary Monthly Safety Report 6 30-APR-2021 through 31-May-2021

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classified as BC Level 1 (confirmed), 24 cases as BC level 2 (probable), 31 cases as BC level 3 (possible).

The majority of the confirmed, probable and possible myocarditis case reports were in younger age groups below 39 years of age (48/73; 66%). None had a fatal outcome. There were more males than females. 2 cases assessed as possible myocarditis were from Canada.

Canadian cases

Canada vigilance database/CAEFISS database

Reports from the CAEFISS database up to May 2021 showed a statistical signal in all 5 statistical signal detection methods used to assess safety data.

As of June 21, 2021, 66 cases of myocarditis and/or pericarditis have been reported to the Canadian databases following the mRNA vaccines (51/66 Pfizer). Of the 66 patients, 9 have fully recovered, 14 were recovering and 28 had not yet recovered. These cases are currently being assessed for causality. The data is also being analyzed to assess emerging patterns relating to time onset, age/sex patterns.

British Columbia for Centre Disease

On June 24, the British Columbia Centre for Disease Control noted in their Adverse Events Following Immunization with COVID-19 Vaccines report³¹ 18 reports of pericarditis/myocarditis.

Eight individuals had a diagnosis of pericarditis alone, four had myocarditis, and six had myopericarditis. Ages ranged from 16 to 95, and 12 were male. Six had received Moderna vaccine, 10 had Pfizer vaccine, and two had AstraZeneca; two of the events occurred after a second dose (one Pfizer and one Moderna). Some had alternate explanations including rheumatic diseases or genetic syndrome associated with cardiac disorders. One met the diagnostic criteria to be considered a definite case according to the draft Brighton Collaboration myocarditis case definition.

News reports

On June 23, 2021, the Toronto Sun reported that SickKids Hospital has seen “approximately five” cases of myocarditis in youth following vaccination and at least 2 children at McMaster Children’s Hospital³².

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³¹ BCDC COVID-19 vaccine/AEFI reports/COVID19 AEFI Weekly Report 2021-06-24

³² SickKids reports seeing post-vaccine myocarditis in kids | Toronto Sun

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Of note, the SickKids Hospital published clinical considerations, including recommendations for clinicians regarding myocarditis cases on June 16, 2021³³ and noted that the Public Health Ontario has received reports of a small number of cases of myocarditis/pericarditis in the 12-17 age group in Ontario. No further information was provided regarding these cases, however the SickKids fact sheet noted that internationally reported cases experienced mild illness, responded well to conservative treatment and rest, and their symptoms improved quickly.

The published clinical considerations and recommendations included symptoms to look for; course of action to follow; status update of previously reported cases; treatment, follow-up; follow-up for long-term complications; criteria to use to rule out the possibility of Multi-Inflammatory Syndrome. The Sick Kids Hospital noted that further guidance will be issued regarding the administration of a second dose to a patient who has developed myocarditis/pericarditis following the first dose.

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International Cases*Israel*

The Israel Ministry of Health confirmed a probability for a possible link between the second vaccine dose and the onset of myocarditis among young men aged 16 to 30. This link was found to be stronger among the younger age group, 16 to 19, compared to other age groups. This link became weaker the older the vaccinated individual is. In most cases myocarditis took the form of mild illness that passed within a few days.

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United States

As per the data from the CDC in the United States most confirmed cases have occurred mostly in male adolescents and young adults age 16 years or older, more often after getting the second dose than after the first dose of one of the mRNA vaccine and the condition is typically seen within several days after COVID vaccination. These cases are rare in the context of global immunization and millions of vaccine doses administered.

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*Switzerland (Swissmedic)***Spontaneous reports from Switzerland**

- 5 million doses administered (as at the start of June 2021)
- Reported cases up to May 27, 2021:
 - 12 reports: Myocarditis (2), Perimyocarditis³⁴ (4), Pericarditis (6)
 - Reporting rate 1:400,000 vaccine doses
 - Women (3), Men (8), Unk (1)
 - Average age s 47 (range 18-70)

³³Reports of myocarditis/pericarditis after COVID-19 vaccination. SickKids Hospital-Clinical Considerations

³⁴ With overlaps between these clinical presentations

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- PfizerBionTech (4), Moderna (7), Unk (1)
- After D1 (9), after D2 (3)
- Time to onset 8.75 days (range 1-28 days)
- 5/12 patients had a history of relevant illnesses (chronic kidney disease, kidney transplant, myelodysplastic syndrome, recurrent pericarditis (now with reported pericarditis after vaccination).
- 1/12 death reported (67 yo, M, pre-existing heart disease and renal failure requiring dialysis)
- *As can be ascertained from the documentation, most of the other patients experienced a fairly mild episode, or else the final details on the outcome of the illness are not yet available.*

Conclusion

- Whether a causal link actually exists between the mRNA vaccines and these reactions is currently classed as *unclear internationally in view of the low reporting rate, the low background incidence of the disease and the clinical complexity of the reported cases.*
- In any case, healthcare professionals should consider this tentative diagnosis when symptoms that are compatible with a myocarditis/pericarditis, but were not caused by other heart diseases, occur in individuals shortly after a vaccination.
- Swissmedic will provide further information or introduce risk minimisation measures without delay if any new aspects come to light.

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Singapore (HAS) published on June 11, 2021 (Expert Committee on COVID-19 Vaccination)³⁵

- Increased occurrences of myocarditis and pericarditis after the second dose observed in Israel and US in males below the age of 25 years.
- Risk estimated at 1.6 case per 100000 doses in the US, comparable to the risk of anaphylaxis observed in Singapore
- To date no observed incremental risk of myocarditis and pericarditis after the first dose of vaccine

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Spontaneous reports from Singapore

- 4 reports in young men
- Age range 18 to 30 years
- At the upper end of the expected range for this age group, based on background incidence rates
- Most cases occurred after a few days of the 2nd dose (D2)
- All have recovered or have been discharged well from hospital

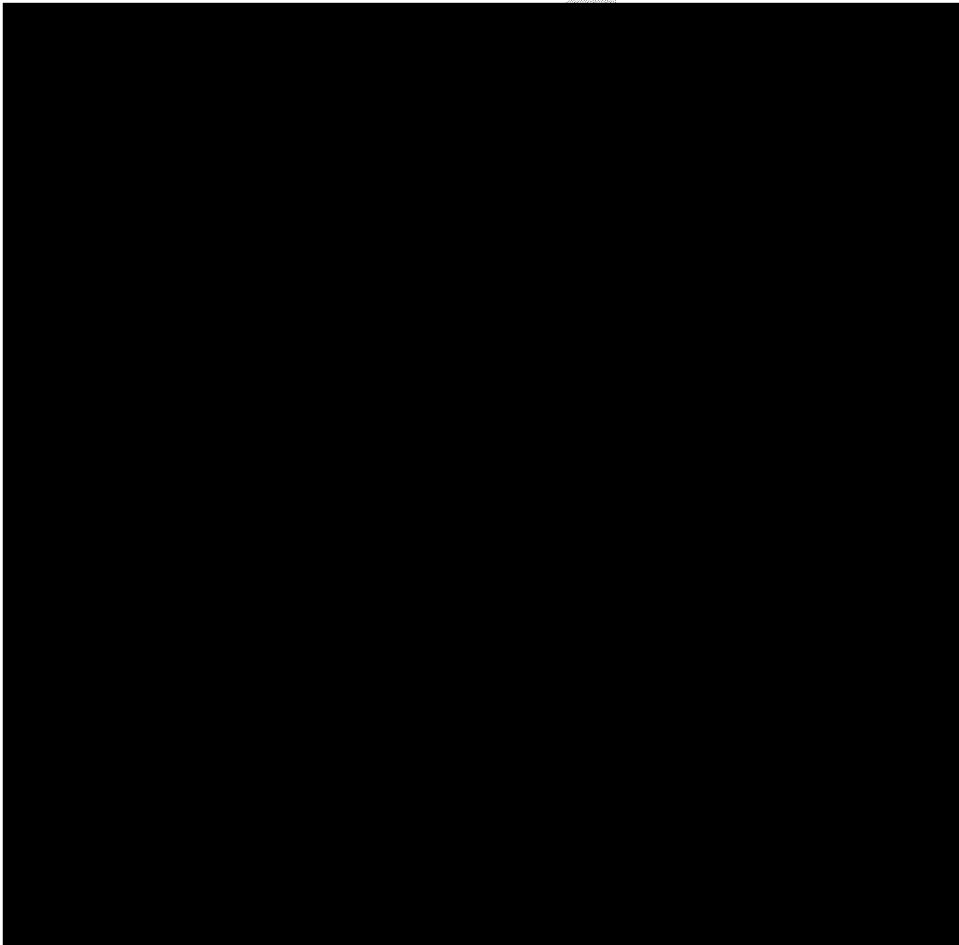
³⁵ MOH | News Highlights

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Conclusion

- While further studies and investigations are on-going, the currently available data suggests that there may be a very small risk of myocarditis and pericarditis after the second dose of an mRNA vaccine, particularly in young men.
- As a precaution, EC19V recommends that vaccinated persons, in particular adolescents and younger men, should avoid strenuous physical activity for one week after their second dose. During this time, they should seek medical attention promptly if they develop chest pain, shortness of breath or abnormal heartbeats
- EC19V will continue to monitor the available data



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EMA PRAC meeting (meeting held on June 07, 2021)

- EMA data: based on Eudravigilance data assessment including an Observed/Expected analysis of myocarditis; a statistically disproportionate reporting was observed which was estimated to be 5 times higher in younger populations for all COVID vaccines for the signal of myocarditis. The signal was stronger in male patients; however, a signal was also detected in female patients in the younger age groups.
- The EMA PRAC decided to initiate a safety signal regarding this risk with accelerated timelines.
- During the meeting, Israel shared their estimate incidence data: estimated incidence of myocarditis in the 16 to 19 years of age following vaccination is about 1 case in 6000 vaccinated individuals.
- Signal to go ahead separately from MSSR (with shorter timelines to be able to have maximal regulatory impact)-considerations to terms will be taken into account (myocarditis and or pericarditis)

End of Confidential Information

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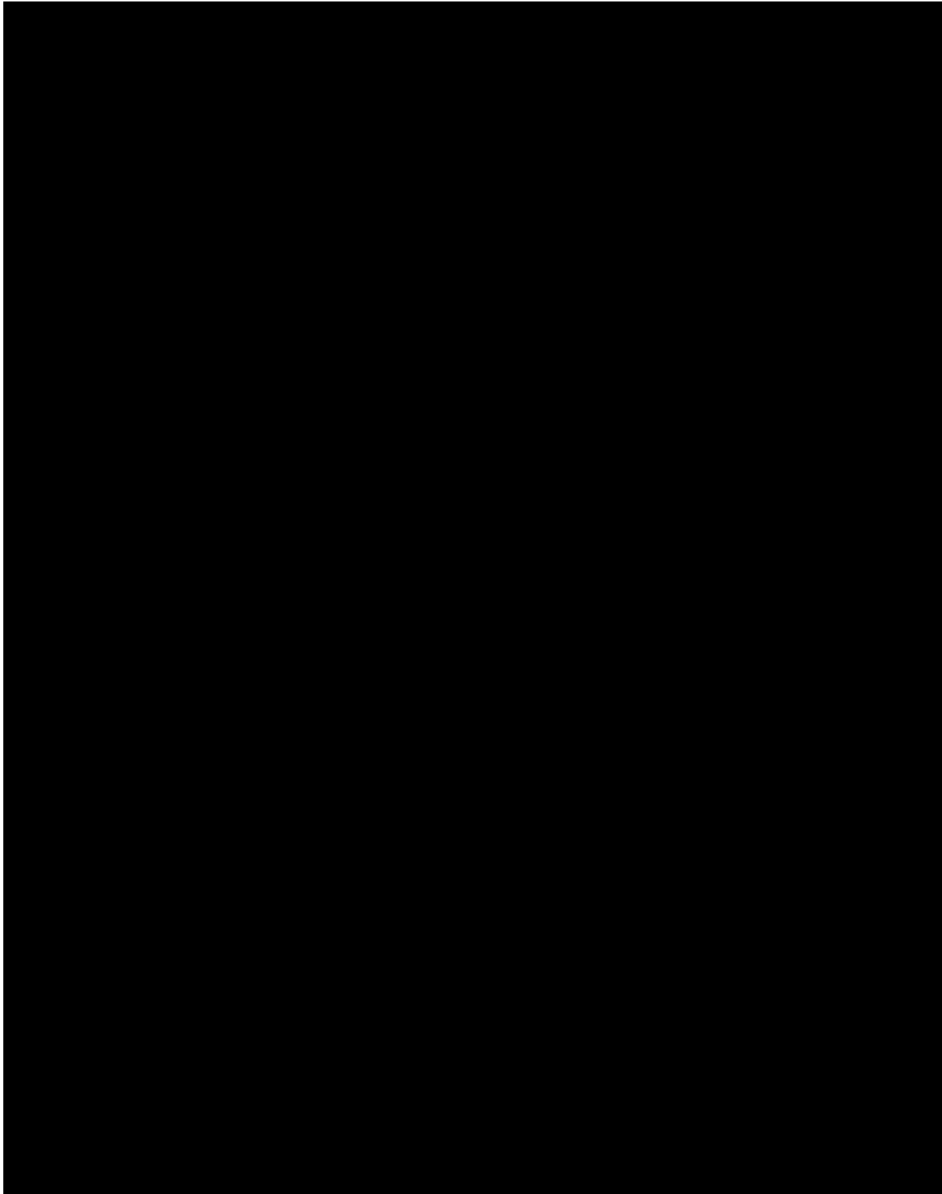
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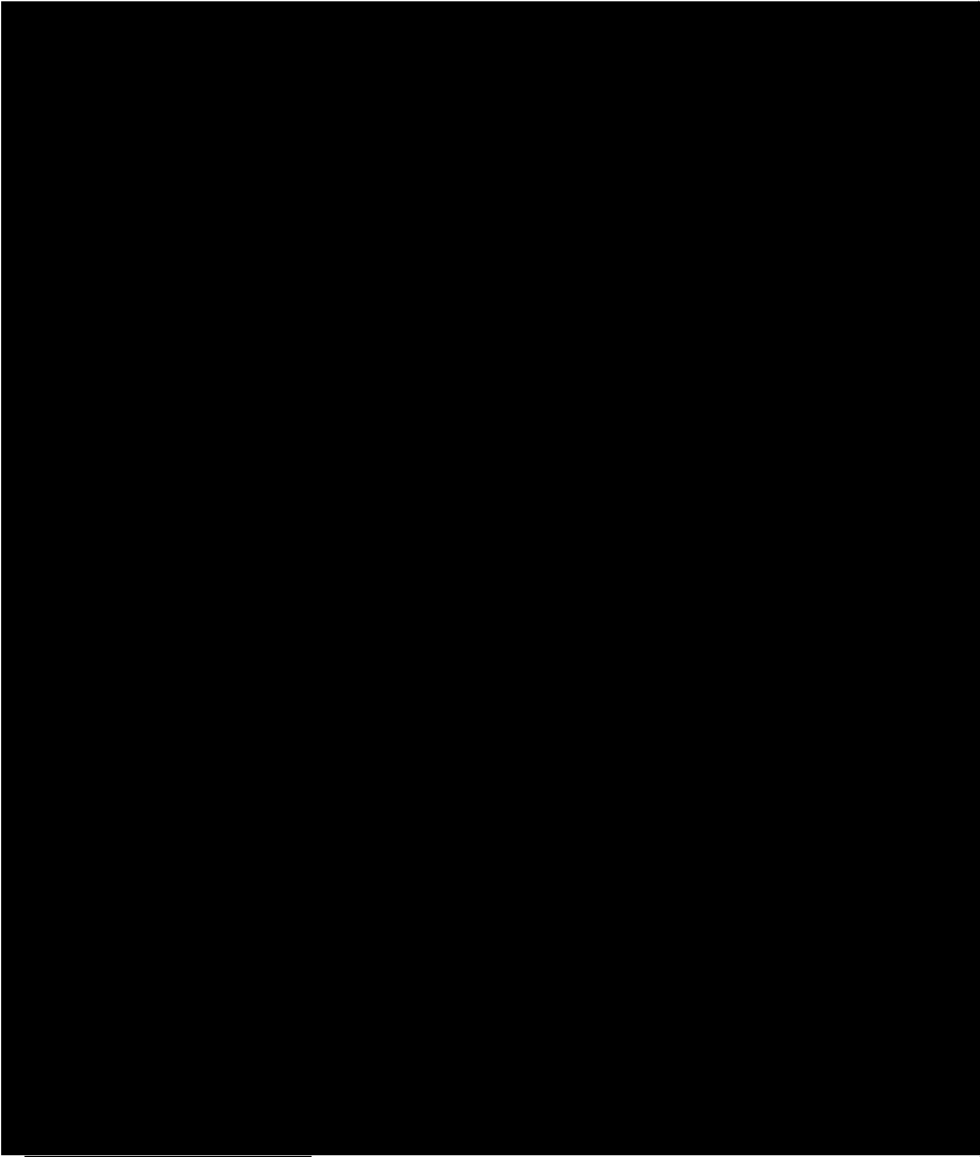
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³⁶ Laufer-Perl M, Havakuk O, Shacham Y, et al. Sex-based differences in prevalence and clinical presentation among pericarditis and myopericarditis patients. *Am J Emerg Med.* 2017;35(2):201-205. doi:10.1016/j.ajem.2016.10.039
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Scientific and medical literature

Analysis of Individual Case reports found in the literature

The patterns from international reporting have been also confirmed in at least 8 case reports/series published in the scientific and medical literature in the last 2 weeks. 8 case reports of potential interest for myocarditis were retrieved from an ongoing literature search.

1. Symptomatic Acute Myocarditis in Seven Adolescents Following Pfizer-BioNTech COVID-19 Vaccination (Marshall et al, 2021)³⁹

Summary

- 7 male patients (14 to 19 years old) (US)
- Myocarditis or myopericarditis 2-4 days after D2
- 6/7 no history of COVID-19 infection or another viral cause of inflammation
- Reported Symptoms: chest pain (7), fever (5), shortness of breath, fatigue, pain in both arms, nausea, vomiting, headache, anorexia and weakness
- Diagnosis: elevated troponin levels/abnormal electrocardiogram/cardiac MRI results
- Treatment: NSAIDs only (3), IV immune globulin and corticosteroids (4)
- All recovered (within 2-6 days)
- Note (authors): Myocarditis onset shorter than myocarditis onset linked to smallpox vaccine

³⁷ Slide 29 (dataset up to June 11, 2021, Tom Shimabukuro, MD, MPH, MBA) from the Advisory Committee on Immunization Practices, June 23, 2021 ACIP June 23, 2021, CDC COVID-19 Vaccine Task Force

³⁸ [Israel reports link between rare cases of heart inflammation and COVID-19 vaccination in young men | Science | AAAS \(sciencemag.org\)](#)

³⁹ Marshall M, Ferguson ID, Lewis P, et al. Symptomatic acute myocarditis in seven adolescents following Pfizer-BioNTech COVID-19 vaccination. *Pediatrics*. 2021; doi: 10.1542/peds.2021-052478 (Case report)

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- Conclusion (authors): *Causality not established but temporal association with vaccination, striking similarity in the clinical and laboratory presentations raise the possibility for such a relationship*
2. Myocarditis after SARS-CoV-2 Vaccination: A Vaccine-induced Reaction? (D'Angelo et al, 2021)⁴⁰

Summary

- 30 year old male (Italy)
 - Myocardopericarditis 72 hours after D2 (given 21 days after D1)
 - Tested negative for COVID-19, family history negative for rheumatological or genetic diseases
 - Diagnosis: MRI/ECG and laboratory results
 - Treatment: bisoprolol and acetylsalicylic acid, prednisolone
 - Cardiac specific troponin levels progressively decreased, discharged home 7 days after hospitalization
 - Conclusion (authors): *in our case, we speculate that adverse reaction against the COVID-19 vaccine was responsible for the development of myocarditis due to its temporal relationship. However, substantial evidences other than temporal aspects still need to be provided to demonstrate the causality, such as histologically proven cases of autoimmune myocarditis following vaccination.*
3. In Depth Evaluation of a Case of Presumed Myocarditis Following the Second Dose of COVID-19 mRNA Vaccine (Muthukumar et al, 2021)⁴¹

Summary

- 50 year-old healthy male
 - Presumptive diagnosis of myocarditis 3 days after Dose 2 (Moderna)
 - Conclusion (authors): *The case does not prove a causal association between the vaccine and the observed myocarditis-like syndrome. However, ischemic injury and other potential causes of acute myocardial injury were excluded, as were other potential infectious causes of myocarditis, and there was no evidence of systemic autoimmune disease. The lack of evidence for upregulation of IL17 cytokine, combined with the increased NK cell numbers observed in the case patient, could suggest a distinct vaccine-associated immunophenotype with a high likelihood for rapid recovery. However, it is not clear whether the observed differences reflect a potential (causal) pathologic immune response or rather appropriate healing responses to myocardial inflammation*
4. Myocarditis Temporally Associated with COVID-19 Vaccination (Rosner et al, 2021)⁴²

⁴⁰ Case report. Myocarditis after SARS-CoV-2 Vaccination: A Vaccine-induced Reaction?

⁴¹ Case report. Presumed Myocarditis Following the Second Dose of COVID-19 mRNA Vaccine

⁴² Case-series (7 patients). Myocarditis after COVID-19 Vaccination

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Summary

- 7 male patients (US) below 40 years of age
- 6 patients received mRNA vaccines (Moderna or Pfizer)
- Myocarditis 3-7 days post vaccination
- Symptoms: acute onset chest pain
- Diagnosis: elevated troponin, ECG and cardiac magnetic resonance
- Medical history: None had evidence of an active viral illness or autoimmune disease and 6/7 had negative PCR testing. Assessment of COVID19 serology was obtained for 6/7 patients, with 4/6 showing presence of spike protein IgG antibodies.
- Treatment varied and included beta-blocker and anti-inflammatory medication
- Outcome: all recovered/symptoms resolved following 3±1 days
- Conclusion (authors): *Our series of 7 male COVID-19 vaccination recipients who presented with myocarditis-like illness supports a potential causal association with vaccination given the temporal relationship, clinical presentation and CMR findings. The clinical course of vaccine-associated myocarditis-like illness appears favorable, with resolution of symptoms in all patients. Given the potential morbidity of COVID-19 infection even in younger adults, the risk-benefit decision for vaccination remains highly favorable.*

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5. Summary

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6. Considerations:

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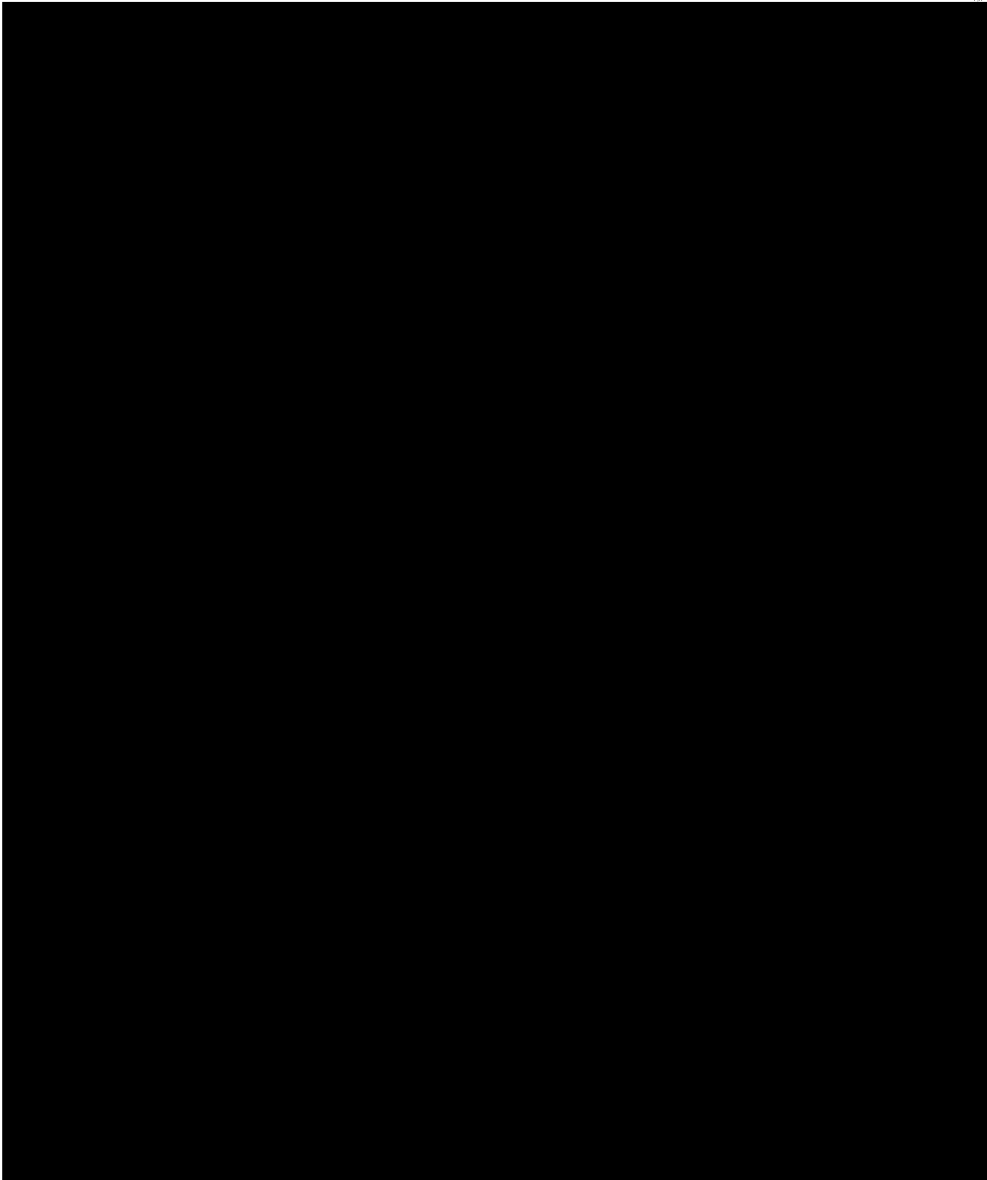
7. Recommendations:

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Cardiovascular

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Myocarditis and Pericarditis

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8. Managers

Scientific Medical

☐ ☐ Recommend for approval

Comment: (Include any concerns regarding differences in Scientific and/or medical opinion.)

9. Director

Agree: ☐ Disagree: ☐

Comment: (recommend either a formal Dissent process or written justification for agreement or disagreement with a recommendation from the manager(s) clearly stating what the Director is agreeing or disagreeing with.)

10. References:

- Included as footnotes throughout the document

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To: [REDACTED]@pfizer.com"; [REDACTED]@Pfizer.com"
Cc: Panetta, Vincent (HC/SC); Eassa, Samar (HC/SC)
Bcc: Fung2, Winnie (HC/SC); HC.F ORA COVID / BAR COVID F.SC; Ali, Osman (HC/SC)
Subject: URGENT: Advisement Letter for Pfizer-BioNTech COVID 19 Vaccine [Control No. 254700]
Date: 2021-07-14 10:58:00 AM
Attachments: 254700 Advisement Letter PFIZER Covid-19 vaccine 14 July 2021.pdf
Importance: High

Dear [REDACTED]

Please find attached the Advisement Letter requesting revisions to the Canadian Product Monograph of **Pfizer-BioNTech COVID 19 Vaccine (COVID-19 mRNA Vaccine) [Control #254700]**, for response **by 9am EST on Wednesday, July 21, 2021.**

This correspondence and attachment is being sent to you via email only. Should you have any questions or need for clarification in this matter, please do not hesitate to contact myself or :

Vincent Panetta
Regulatory Affairs Supervisor
Office of Regulatory Affairs
vincent.panetta@canada.ca
Tel: 613-866-0148
Fax: 613-946-9520

Please acknowledge receipt by responding to this email at your earliest convenience.

Kind regards,

Osman Ali
Post Market Coordinator
Office of Regulatory Intelligence and Risk Management
Center for Regulatory Excellence, Statistics and Trials
NEW* Biologic and Radiopharmaceutical Drugs Directorate (BRDD)
Health Products and Food Branch
Health Canada / Government of Canada
osman.ali@canada.ca
+1 343 548 2519

Bureau du renseignement réglementaire et de la gestion du risque
Centre d'Excellence Réglementaire, de Statistiques et Essais Cliniques (CERES)
*NOUVEAU : Direction des médicaments biologiques et radiopharmaceutiques (DMBR)
Direction générale des produits de santé et des aliments
Santé Canada / Gouvernement du Canada
osman.ali@canada.ca
+1 343 548 2519

Health
CanadaSanté
CanadaHealth Products
and Food BranchDirection générale des produits
de santé et des aliments

Biologic and Radiopharmaceutical
Drugs Directorate
100 Eglantine Driveway
Address Locator #0601C
Ottawa, Ontario
K1A 0K9

July 14, 2021

Dossier ID: HC6-024-243022**Control #: 254700****Document #: 1697500**

[REDACTED]
[REDACTED] - Regulatory Affairs
BioNTech Manufacturing GMBH
c/o Pfizer Canada ULC
17300 Trans-Canada Highway
Kirkland, Quebec, Canada H9J 2M5
Email: [REDACTED]@pfizer.com

RE: Request for Amendment to support labelling changes for Pfizer-BioNTech COVID 19 Vaccine (COVID-19 mRNA Vaccine) pursuant to section 21.2 of the *Food and Drugs Act*

Dear [REDACTED]

As part of Health Canada's efforts to minimize health risk factors to Canadians while maximizing the safety provided by the regulatory system for health products, the Marketed Health Products Directorate (MHPD) and the Biologic and Radiopharmaceutical Drugs (BRDD) have reviewed the fifth Summary Monthly Safety Report-SMSR, submitted under sequence 0122 and the sixth SMSR, submitted under sequence 0133, for the **PFIZER-BIONTECH COVID-19 Vaccine**.

Health Canada is hereby requesting the sponsor to update the labelling information for **Pfizer-BioNTech COVID-19 Vaccine (COVID-19 mRNA Vaccine)** with respect to new safety information concerning facial paralysis.

We invite you to revise the Product Monograph to reflect the following suggested revisions:

1. Please add the following text concerning acute facial paralysis under section **8.2 Clinical Trial Adverse Reactions**, Unsolicited Adverse Events, *Serious Adverse Events*

Through the clinical trial safety follow-up period to 14 November 2020, acute peripheral facial paralysis (or palsy) was reported by four participants in the Pfizer – BioNtech COVID-19 Vaccine group. Onset was Day 37 after Dose 1 (participant did not receive Dose 2) and Days 3, 9, and 48 after Dose 2. No cases of acute peripheral facial paralysis (or palsy) were reported in the placebo group.

2. As frequency has not been assessed in Canada, the addition of facial paralysis / Bells palsy as unknown frequency under section **8.3 Post Market Adverse Reaction** is recommended:

Nervous System Disorders: facial paralysis / Bell's Palsy

3. Please add the following sentence in the PATIENT MEDICATION INFORMATION section, below **"What are possible side effects from using Pfizer-BioNTech COVID-19 Vaccine?"**, underneath **"Uncommon"**:

Non-severe allergic reactions (such as rash, itching, hives or swelling of the face), severe allergic reactions, and facial paralysis / Bell's palsy have been reported.

4. The sponsor is also requested to update the Canadian Product Monograph to align with the Company Data Sheet (CDS) including but not limited to the following events: Asthenia, Lethargy, Decreased appetite, Hyperhidrosis, Night sweats, Paresthesia, Tachycardia and Hypoesthesia.

It is requested that the current and revised Product Monograph be provided electronically. The sponsor is also requested to update any impacted inner and/or outer label elements, including applicable company website materials, to align with the Product Monograph revisions accordingly. No changes other than those indicated in this letter may be made in your filing.

Please respond to this letter by filing an **Amendment** to the Application, filed under section 3 of the Interim Order Respecting the Importation, Sale and Advertising of Drugs for Use in Relation to COVID-19, no later than **9am EST on Wednesday, July 21, 2021**.

The applicable control number is listed on the first page of this letter. A copy of this letter should be attached to your covering letter for the Amendment. The Amendment, including electronic copies of both the annotated and non-annotated Product Monograph, as well as revised labelling elements (if applicable), should be prepared and submitted in the usual manner as per the *Guidance for Industry: Preparation of Drug Submissions in Electronic Common Technical Document (eCTD) Format*.

Should you not agree with Health Canada's findings and/or proposed changes, you are invited to make representations explaining why a change to the label of this drug is not required or how other changes you propose are adequate to address the risks identified. You have until **9am EST on Wednesday, July 21, 2021** to provide written representations outside of the Amendment process. Health Canada will review the written representations to determine whether a label change is still required. If, following these discussions and review, Health Canada still considers that the Amendment is required to update the labelling of Pfizer-BioNTech COVID-19 Vaccine (COVID-19 mRNA Vaccine), we will inform you accordingly.

Failure to respond to this letter **9am EST on Wednesday, July 21, 2021** with either representations or Amendment filing may result in the Minister issuing an Order pursuant to

section 21.2 of the *Food and Drugs Act (FDA)* without further notice to you. In accordance with section 21.4(2), Orders and reasons for issuance are made publically available.

No amendment other than the ones dealing with the present subject matter will be considered at this point. If you have other issues which require review, please contact the Regulatory Affairs Supervisor to discuss sequencing of submissions. Your co-operation with this requirement is appreciated and will facilitate review of these important safety updates.

If you are unable to comply with this request for any reason, or if you have any question in this matter, please contact the following directly as soon as possible:

Vincent Panetta
Regulatory Affairs Supervisor
Office of Regulatory Affairs
Tel: 613-866-0148
Fax: 613-946-9520

Please note that the contents of this letter have been determined and agreed to by a collaborative effort of the Directorates involved in the federal regulatory activities pertaining to this product.

Sincerely,

This document has been signed electronically using the Health Canada docuBridge system.

Léo Bouthillier
Director
Centre for Evaluation of Radiopharmaceuticals and Biotherapeutics (CERB)
Biologic and Radiopharmaceutical Drugs Directorate (BRDD)

From: BRDD.Risk / risque.DMBR (HC/SC)
To: [REDACTED]@pfizer.com"
Cc: Panetta, Vincent (HC/SC); Eassa, Samar (HC/SC); [REDACTED]@Pfizer.com"
Bcc: Fung2, Winnie (HC/SC); HC.F ORA COVID / BAR COVID F.SC
Subject: URGENT: Advisement Letter for Pfizer-BioNTech COVID 19 Vaccine [Control No. 254161]
Date: 2021-06-25 6:08:00 PM
Attachments: 254161 Advisement Letter PFIZER Covid-19 vaccine 25 JUN 2021.pdf
Importance: High

Dear [REDACTED]

Please find attached the Advisement Letter requesting revisions to the Canadian Product Monograph of **Pfizer-BioNTech COVID 19 Vaccine (COVID-19 mRNA Vaccine) [Control #254161]**, for response **by 12pm EST on Monday, June 28, 2021.**

This correspondence and attachment is being sent to you via email only. Should you have any questions or need for clarification in this matter, please do not hesitate to contact myself or :

Vincent Panetta
Regulatory Affairs Supervisor
Office of Regulatory Affairs
vincent.panetta@canada.ca
Tel: 613-866-0148
Fax: 613-946-9520

Please acknowledge receipt by responding to this email at your earliest convenience.

Kind regards,

Winnie Fung, MASc.

Senior Regulatory Advisor, Risk Issues Management
Office of Regulatory Intelligence and Risk Management
Biologic and Radiopharmaceutical Drugs Directorate (BRDD)
winnie.fung2@canada.ca | Tel: 343-574-5368

Conseillère principale en réglementation en gestion du risque
Bureau du renseignement réglementaire et de la gestion du risque
Direction des médicaments biologiques et radiopharmaceutiques (DMBR)
winnie.fung2@canada.ca | Tél: 343-574-5368

Health
CanadaSanté
CanadaHealth Products
and Food BranchDirection générale des produits
de santé et des aliments

Biologic and Radiopharmaceutical
Drugs Directorate
100 Eglantine Driveway
Address Locator #0601C
Ottawa, Ontario
K1A 0K9

June 25, 2021

Dossier ID: HC6-024-243022**Control #: 254161****Document #: 1691841**

[REDACTED] Regulatory Affairs
BioNTech Manufacturing GMBH
c/o Pfizer Canada ULC
17300 Trans-Canada Highway
Kirkland, Quebec, Canada H9J 2M5
Email: [REDACTED]@pfizer.com

RE: Request for Amendment to support labelling changes for Pfizer-BioNTech COVID 19 Vaccine (COVID-19 mRNA Vaccine) pursuant to section 21.2 of the *Food and Drugs Act*

Dear [REDACTED]

As part of Health Canada's efforts to minimize health risk factors to Canadians while maximizing the safety provided by the regulatory system for health products, the Marketed Health Products Directorate (MHPD) and the Biologic and Radiopharmaceutical Drugs (BRDD) have reviewed the post-market safety data available to date for mRNA vaccines and the risk of myocarditis and pericarditis, including Canadian data and emerging information from international jurisdictions.

Health Canada is hereby requesting the sponsor to update the labelling information for **Pfizer-BioNTech COVID-19 Vaccine (COVID-19 mRNA Vaccine)** with respect to new safety information concerning myocarditis and pericarditis.

We invite you to revise the Product Monograph to reflect the following suggested revisions:

1. **Include**, in "7 WARNINGS AND PRECAUTIONS" immediately after the "Acute Allergic Reactions" section, the following text in a new section with the heading "Cardiovascular:"

Cardiovascular

Myocarditis and Pericarditis

Cases of myocarditis and/or pericarditis following vaccination with Pfizer-BioNTech COVID-19 Vaccine have been reported during post-authorization use. These cases occurred more commonly after the second dose and in adolescents and young adults. Typically, the onset of symptoms has been within a few days following receipt of the Pfizer-BioNTech COVID-19 Vaccine. Available short-term follow-up data suggest that the symptoms resolve in most individuals, but information on long-term sequelae is lacking. The decision to administer the Pfizer-BioNTech COVID-19 Vaccine to an individual with a history of myocarditis or pericarditis should take into account the individual's clinical circumstances.

Healthcare professionals are advised to consider the possibility of myocarditis and/or pericarditis in their differential diagnosis when individuals present with chest pain, shortness of breath, palpitations or other signs and symptoms of myocarditis and/or pericarditis following immunization with a COVID-19 vaccine. This could allow for early diagnosis and treatment. Cardiology consultation for management and follow up should be considered.

2. **Include**, in “8.3 Post-Market Adverse Reactions,” immediately after the sentence “The following adverse reactions have been identified during post authorization use of Pfizer-BioNTech COVID-19 Vaccine,” the following new text:

Cardiac disorders: myocarditis and/or pericarditis (see WARNING and PRECAUTIONS)

3. **Include**, in “PATIENT MEDICATION INFORMATION,” under the section beginning with “To help avoid side effects and ensure proper use...,” after the bullet “have a weakened immune system due to a medical condition or are on a medicine that affects your immune system,” the following new text:

- have previously had episodes of myocarditis and/or pericarditis

It is requested that the current and revised Product Monograph be provided electronically. The sponsor is also requested to update any impacted inner and/or outer label elements, including applicable company website materials, to align with the Product Monograph revisions accordingly. No changes other than those indicated in this letter may be made in your filing.

Please respond to this letter by filing an **Amendment** to the Application, filed under section 3 of the Interim Order Respecting the Importation, Sale and Advertising of Drugs for Use in Relation to COVID-19, no later than **12:00pm EST on Monday, June 28, 2021**.

The applicable control number is listed on the first page of this letter. A copy of this letter should be attached to your covering letter for the Amendment. The Amendment, including electronic copies of both the annotated and non-annotated Product Monograph, as well as revised labelling elements (if applicable), should be prepared and submitted in the usual manner as per the

Guidance for Industry: Preparation of Drug Submissions in Electronic Common Technical Document (eCTD) Format.

Should you not agree with Health Canada's findings and/or proposed changes, you are invited to make representations explaining why a change to the label of this drug is not required or how other changes you propose are adequate to address the risks identified. You have until **12:00pm EST on Monday, June 28, 2021** to provide written representations outside of the Amendment process. Health Canada will review the written representations to determine whether a label change is still required. If, following these discussions and review, Health Canada still considers that the Amendment is required to update the labelling of Pfizer-BioNTech COVID-19 Vaccine (COVID-19 mRNA Vaccine), we will inform you accordingly.

Failure to respond to this letter **12:00pm EST on Monday, June 28, 2021** with either representations or Amendment filing may result in the Minister issuing an Order pursuant to section 21.2 of the *Food and Drugs Act (FDA)* without further notice to you. In accordance with section 21.4(2), Orders and reasons for issuance are made publically available.

No amendment other than the ones dealing with the present subject matter will be considered at this point. If you have other issues which require review, please contact the Regulatory Affairs Supervisor to discuss sequencing of submissions. Your co-operation with this requirement is appreciated and will facilitate review of these important safety updates.

If you are unable to comply with this request for any reason, or if you have any question in this matter, please contact the following directly as soon as possible:

Vincent Panetta
Regulatory Affairs Supervisor
Office of Regulatory Affairs
Tel: 613-866-0148
Fax: 613-946-9520

Please note that the contents of this letter have been determined and agreed to by a collaborative effort of the Directorates involved in the federal regulatory activities pertaining to this product.

Sincerely,

This document has been signed electronically using the Health Canada docuBridge system.

Léo Bouthillier
Director
Centre for Evaluation of Radiopharmaceuticals and Biotherapeutics (CERB)
Biologic and Radiopharmaceutical Drugs Directorate (BRDD)

**CUMULATIVE ANALYSIS OF CARDIAC FAILURE AND MYOCARDIAL
INFARCTION ADVERSE EVENT REPORTS OF PF-07302048 (BNT162B2)
RECEIVED THROUGH 29-APR-2021**

Report Prepared by:

Worldwide Safety

Pfizer

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LIST OF ABBREVIATIONS

Acronym	Term
AE	adverse event
AERs	adverse event reports
COVID-19	coronavirus disease 2019
MAH	Marketing Authorisation Holder
MedDRA	medical dictionary for regulatory activities
PM	Post-Marketing
PT	(MedDRA) Preferred Term
SMSR	Summary Monthly Safety Report
UK	United Kingdom
US	United States

1. INTRODUCTION

Reference is made to the Request from Health Canada for Pfizer/BNT COVID-19 Vaccine (BNT162b2) to provide a:

“Cumulative review of the reports of cardiac failure and myocardial infarction received by Pfizer, including an assessment of the causality to the Pfizer-BioNTech COVID-19 Vaccine.”

2. METHODOLOGY

Pfizer is responsible for the management of post-authorization safety data on behalf of the MAH BioNTech according to the Pharmacovigilance Agreement in place. Data from BioNTech are included in the report when applicable.

Pfizer’s safety database contains cases of AEs reported spontaneously to Pfizer, cases reported by the health authorities, cases published in the medical literature, cases from Pfizer-sponsored marketing programs, non-interventional studies, and cases of serious AEs reported from clinical studies regardless of causality assessment.

The limitations of post-marketing adverse drug event reporting should be considered when interpreting these data:

- Reports are submitted voluntarily, and the magnitude of underreporting is unknown. Some of the factors that may influence whether an event is reported include: length of time since marketing, market share of the drug, publicity about a drug or an AE, seriousness of the reaction, regulatory actions, awareness by health professionals and consumers of adverse drug event reporting, and litigation.
- Because many external factors influence whether or not an AE is reported, the spontaneous reporting system yields reporting proportions not incidence rates. As a result, it is generally not appropriate to make between-drug comparisons using these proportions; the spontaneous reporting system should be used for signal detection rather than hypothesis testing.
- In some reports, clinical information (such as medical history, validation of diagnosis, time from drug use to onset of illness, dose, and use of concomitant drugs) is missing or incomplete, and follow-up information may not be available.
- An accumulation of adverse event reports (AERs) does not necessarily indicate that a particular AE was caused by the drug; rather, the event may be due to an underlying disease or some other factor(s) such as past medical history or concomitant medication.

An evaluation of the cardiac failure and myocardial infarction adverse event reports occurring after BNT162b2 immunization was conducted utilizing a review of reports contained in the Pfizer global safety database.

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2.1. Safety Database

The following search of the post-marketing safety database was performed as of 30 April 2021:

All post-authorisation BNT162b2 cases cumulatively received through 29 April 2021 reporting the (MedDRA) Preferred Terms (PTs): *Myocardial infarction*, *Cardiac failure*, *Acute myocardial infarction*, and *Cardiac failure acute*.

3. RESULTS

It is estimated that approximately 415,922,715 doses of BNT162b2 were shipped worldwide from the receipt of the first temporary authorisation for emergency supply on 01 December 2020 through 29 April 2021.

Cumulatively, through 29 April 2021, there was a total of 109,692 case reports (61,946 medically confirmed and 47,746 non-medically confirmed) containing 415,068 events in the global safety database for BNT162B2.

Of these, 726 cases (0.7 %) were retrieved by the search described in Section 2.1 (8 medically confirmed and 237 non-medically confirmed).

Table 1 below presents the main characteristics of the 726 cases.

Table 1. General Overview

	Characteristics	Relevant cases (N=726)
Gender:	Female	394
	Male	321
	No Data	11
Age range (years): 23 -104 years Mean = 77.8 years n = 697	18-30	8
	31-50	49
	51-64	83
	65-74	92
	≥ 75	470
	Unknown	24
Case outcome:	Recovered/Recovering	204
	Recovered with sequelae	35
	Not recovered at the time of report	112
	Fatal	300
	Unknown	75
Relevant PTs	Myocardial infarction	319
	Cardiac failure	283
	Acute myocardial infarction	121
	Cardiac failure acute	26

Table 2 below presents an analysis of the adverse event reports retrieved for each PT.

Table 2. Cardiac failure and myocardial infarction adverse event reports analysis for BNT162b2

Selected PT	Post-Marketing Cases Evaluation
Myocardial infarction	<ul style="list-style-type: none"> • Number of cases: 319 (0.3% of the total PM dataset), of which 3 are medically confirmed and 171 are non-medically confirmed; • Country of incidence: US (100), UK (86), France (36), Netherlands (20), Sweden (13), Germany (10), Israel (7), Italy (5), Austria (4), Czech Republic and Greece (3 each), Canada, Costa Rica, Cyprus, Finland, Ireland, Japan, Mexico, Norway, Poland, Slovenia and Spain (2 each); the remaining 10 cases were distributed among 10 other countries; • Subjects' gender: female (172), male (140) and unknown (7); • Subjects' age group (n = 292): Adult (80), Elderly (217) unknown (22); • Event seriousness: serious (319); • Relevant event outcome: fatal (108), resolved/resolving (74), resolved with sequelae (20), not resolved (31) and unknown (86); • Myocardial infarction (319) was co-reported with Cardiac failure in 14 cases, with Cardiac failure acute in 2 cases, and with Acute myocardial infarction in 2 cases • Most co-reported PTs (≥ 9 occurrences): Chest pain (51), Dyspnoea (39), Malaise (33), Fatigue (27), Pain in extremity (25), Nausea (21), Headache, Pyrexia and Pain (19 each), Dizziness (16), Vomiting (15), Arthralgia and Cardiac failure (14 each), Asthenia, Cerebrovascular accident, Chest discomfort, Thrombosis (13 each), Chills, Hypertension and Vaccination site pain (12 each), Back pain, Death, and Diarrhoea (10 each), Cardiac arrest, Fall, Heart rate increased, Loss of consciousness, Pulmonary oedema and Paraesthesia (9 each). • Relevant event onset latency (n = 913): Range from <24 hours to 109 days, median 2 days; • Cases with Medical History: 229 • Relevant PTs Medical History (≥ 2): Myocardial infarction (38), Atrial fibrillation (18), Myocardial ischaemia (17), Cardiac disorder (14), Coronary artery disease (12), Cardiac failure (8), Mitral valve incompetence (4), Acute myocardial infarction, Aortic valve incompetence, Hypertensive heart disease and Mitral valve prolapse (3 each), Angina pectoris, Arrhythmia, Bundle branch block left, Cardiac failure congestive and Cardiac valve disease (2 each); • Other relevant history: COVID-19 (15), suspected COVID-19 (2), Coronavirus infection and Asymptomatic COVID-19 (1 each). <p>Conclusion: This cumulative case review does not raise new safety issues. Surveillance will continue.</p>
Acute myocardial infarction	<ul style="list-style-type: none"> • Number of cases: 121 (0.1% of the total PM dataset), of which 1 is medically confirmed and 20 are non-medically confirmed; • Country of incidence: Germany (20), UK (19), Italy (9), Sweden (8), Netherlands, US and Spain (7 each), Denmark, France and Norway (5 each), Israel and Portugal (4 each), Greece and Poland (3 each), the remaining 15 cases were distributed among 11 other countries;

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Table 2. Cardiac failure and myocardial infarction adverse event reports analysis for BNT162b2

Selected PT	Post-Marketing Cases Evaluation
	<ul style="list-style-type: none"> Subjects' gender: female (59), male (60) and unknown (2); Subjects' age group (n = 121): Adult (41), Elderly (80); Relevant event outcome: fatal (46), resolved/resolving (40), resolved with sequelae (5), not resolved (14) and unknown (24); Acute myocardial infarction was co-reported with Myocardial infarction in 2 cases, and with Cardiac failure in 4 cases. Most co-reported PTs (≥ 5 occurrences): Chest pain (22), Malaise (14), Dyspnoea (12), Pyrexia (10), Asthenia, Fatigue and Nausea (7 each), Cardiac arrest (6), Cardiogenic shock, Chills, Pneumonia, Syncope and Vomiting (5 each), Cardiac failure, Cardio-respiratory arrest, Chest discomfort, Circulatory collapse and Incorrect route of product administration (4 each). Relevant event onset latency (n = 359): Range from <24 hours to 24 days, median 1 day; Cases with Medical History: (100) Relevant PTs Medical History (≥ 2): Atrial fibrillation (11), Acute myocardial infarction and Myocardial ischaemia (9 each), Coronary artery disease (8), Myocardial infarction (7), Angina pectoris and Cardiac failure (3 each), Cardiac disorder, Cardiomyopathy and Ischaemic cardiomyopathy (2 each). Other relevant history: COVID-19 (3), Asymptomatic COVID-19 (1). <p>Conclusion: This cumulative case review does not raise new safety issues. Surveillance will continue.</p>
Cardiac failure	<ul style="list-style-type: none"> Number of cases: 283 (0.26% of the total PM dataset), of which 4 are medically confirmed and 52 are non-medically confirmed; Country of incidence: France (87), Germany (39), Netherlands (29), UK (20), Spain (16), Sweden (15), Italy (12), Austria (8), Israel and Finland (7 each), Hungary, Norway, Switzerland and US (5 each), the remaining 23 cases were distributed among 11 other countries; Subjects' gender: female (161), male (119) and unknown (3); Subjects' age group (n = 281): Adult (21), Elderly (260); Event seriousness: serious (283); Relevant event outcome: fatal (122), resolved/resolving (67), resolved with sequelae (6), not resolved (36) and unknown (53); Cardiac failure (283) was co-reported with Myocardial infarction in 14 cases, with Acute myocardial infarction in 4 cases and with Cardiac failure acute in 1 case. Most co-reported PTs (≥ 11 occurrences): Dyspnoea (58), Pyrexia (42), Atrial fibrillation (30), Oxygen saturation decreased (23), Malaise (21), Fatigue (18), Pneumonia and Pulmonary embolism (17 each), Cough, Nausea and Respiratory failure (16 each), Myocardial infarction (14), Asthenia, Cardiac arrest, Hypotension, Oedema peripheral, Renal failure (13 each), Condition aggravated and COVID-19 (12 each), Pleural effusion and Pulmonary oedema (11 each), Arthralgia, Fall and General physical health deterioration (10 each).

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Table 2. Cardiac failure and myocardial infarction adverse event reports analysis for BNT162b2

Selected PT	Post-Marketing Cases Evaluation
	<ul style="list-style-type: none"> Relevant event onset latency (n = 975): Range from <24 hours to 69 days, median 2 days; Cases with Medical History: 242 Relevant PTs Medical History (≥ 3): Atrial fibrillation (86), Cardiac failure (82), Myocardial ischaemia (22), Coronary artery disease and Myocardial infarction (18 each), Arrhythmia (12), Aortic valve stenosis (8), Cardiac failure chronic (6), Cardiac valve disease and Hypertensive heart disease (5 each), Cardiac arrest, Cardiomyopathy and Cardiovascular disorders (4 each), Acute myocardial infarction, Angina pectoris, Aortic valve incompetence, Atrioventricular block, Cardiac disorder, Cardiac failure congestive, Congestive cardiomyopathy, Ischaemic cardiomyopathy, Mitral valve incompetence (3 each). Other relevant history: COVID-19 (31), COVID-19 pneumonia (7), SARS-CoV-2 test positive and Suspected COVID-19 (1 each). <p>Conclusion: This cumulative case review does not raise new safety issues. Surveillance will continue.</p>
Cardiac failure acute	<ul style="list-style-type: none"> Number of cases: 26 cases (0.02% of the total PM dataset), of which 2 are non-medically confirmed; Country of incidence: Spain (7), France (5), Netherlands (4), Japan, Sweden, Switzerland, and UK (2 each), Croatia and Germany (1 each); Subjects' gender: female (12), male (14); Subjects' age group (n=26): Adult (2), Elderly (24); Event seriousness: serious (26); Relevant event outcome: Fatal (13), resolved/resolving (12), unknown (1). Cardiac failure acute was co-reported with Myocardial infarction in 2 cases, and with Cardiac failure in 1 case. Most co-reported PTs (≥ 2 occurrences): Dyspnoea (9), Atrial fibrillation (3), Acute pulmonary oedema, Chills, Condition aggravated, Fatigue, Fluid retention, Hypertension, Hypotension, Malaise, Myocardial infarction, Oedema peripheral, Oxygen saturation decreased, Pneumonia, Pulmonary oedema, Pyrexia and Tachycardia (2 each). Relevant event onset latency (n = 84): Range from <24 hours to 21 days, median 1 day; Cases with Medical History: 24 Relevant PTs Medical History (≥ 2): Atrial fibrillation (7), Cardiac failure (6), Cardiovascular disorder (3), Cardiac disorder, Cardiomyopathy and Mitral valve incompetence (2 each). Other relevant history: COVID-19 (3). <p>Conclusion: This cumulative case review does not raise new safety issues. Surveillance will continue.</p>

4. DISCUSSION

Pfizer performs frequent and rigorous signal detection on BNT162b2 cases. The findings of these analyses are consistent with the known safety profile of the vaccine. This cumulative analysis is an integrated analysis of post-authorization safety data, focused on cardiac failure and myocardial infarction adverse event reports. The data do not support a conclusion that the vaccine causes cardiac failure or myocardial infarction or that labeling changes are warranted.

5. SUMMARY AND CONCLUSION

Review of the available data for this cumulative post authorization experience, confirms a favorable benefit-risk balance for BNT162b2.

Pfizer will continue routine pharmacovigilance activities on behalf of BioNTech according to the Pharmacovigilance Agreement in place, in order to assure patient safety and will inform the Agency if an evaluation of the safety data yields significant new information for BNT162b2.



Life Cycle Management Table

Sponsor Name: BioNTech Manufacturing GmbH					
Brand Name: PFIZER-BIONTECH COVID-19 VACCINE					
Dossier Identifier: e243022					
Sequence Number	Date Submitted	Control Number	Related Sequence	Regulatory Activity Type	Sequence Description
0000	Aug. 28, 2020	---	---	MPNDS	
0001	Sep. 22, 2020	243022	---	MPNDS	
0002	Oct. 07, 2020	243022	0001	MPNDS	
0003	Oct. 09, 2020	244906	---	COVID-19 Interim Order Application	
0004	Nov. 11, 2020	244906	---	MPNDS	
0005	Nov. 12, 2020	244906	0003	COVID-19 Interim Order Application	
0006	Nov. 13, 2020	244906	0003	COVID-19 Interim Order Application	
0007	Nov. 16, 2020	244906	0003	COVID-19 Interim Order Application	
0008	Nov. 20, 2020	244906	0003	COVID-19 Interim Order Application	
0009	Nov. 23, 2020	244906	0003	COVID-19 Interim Order Application	
0010	Nov. 25, 2020	243022	0004	MPNDS	
0011	Nov. 25, 2020	244906	0003	COVID-19 Interim Order Application	



Life Cycle Management Table

Sponsor Name: BioNTech Manufacturing GmbH					
Brand Name: PFIZER-BIONTECH COVID-19 VACCINE					
Dossier Identifier: e243022					
Sequence Number	Date Submitted	Control Number	Related Sequence	Regulatory Activity Type	Sequence Description
0012	Nov. 25, 2020	244906	0003	COVID-19 Interim Order Application	
0013	Nov. 27, 2020	244906	0003	COVID-19 Interim Order Application	
0014	Nov. 30, 2020	244906	0003	COVID-19 Interim Order Application	
0015	Nov. 30, 2020	244906	0003	COVID-19 Interim Order Application	
0016	Nov. 30, 2020	244906	0003	COVID-19 Interim Order Application	
0017	Dec. 01, 2020	244906	0003	COVID-19 Interim Order Application	
0018	Dec. 02, 2020	244906	0003	COVID-19 Interim Order Application	
0019	Dec. 02, 2020	244906	0009	COVID-19 Interim Order Application	
0020	Dec. 04, 2020	244906	0007	COVID-19 Interim Order Application	
0021	Dec. 04, 2020	244906	0013	COVID-19 Interim Order Application	



Life Cycle Management Table

Sponsor Name: BioNTech Manufacturing GmbH					
Brand Name: PFIZER-BIONTECH COVID-19 VACCINE					
Dossier Identifier: e243022					
Sequence Number	Date Submitted	Control Number	Related Sequence	Regulatory Activity Type	Sequence Description
0022	Dec. 04, 2020	244906	0016	MPNDS	
0023	Dec. 04, 2020	244906	0003	COVID-19 Interim Order Application	
0024	Dec. 07, 2020	244906	0003	COVID-19 Interim Order Application	
0025	Dec. 07, 2020	244906	0003	COVID-19 Interim Order Application	
0026	Dec. 08, 2020	244906	0016	COVID-19 Interim Order Application	
0027	Dec. 08, 2020	244906	0022	MPNDS	
0028	Dec. 08, 2020	244906	0018	COVID-19 Interim Order Application	
0029	Dec. 09, 2020	244906	0012	COVID-19 Interim Order Application	
0030	Dec. 09, 2020	244906	0025	COVID-19 Interim Order Application	
0031	Dec. 09, 2020	244906	0018, 0028	COVID-19 Interim Order Application	
0032	Dec. 09, 2020	244906	0031	COVID-19 Interim Order Application	



Life Cycle Management Table

Sponsor Name: BioNTech Manufacturing GmbH					
Brand Name: PFIZER-BIONTECH COVID-19 VACCINE					
Dossier Identifier: e243022					
Sequence Number	Date Submitted	Control Number	Related Sequence	Regulatory Activity Type	Sequence Description
0033	Dec. 10, 2020	244906	0029	COVID-19 Interim Order Application	
0034	Dec. 10, 2020	244906	0013	COVID-19 Interim Order Application	
0035	Dec. 10, 2020	244906	0025	COVID-19 Interim Order Application	
0036	Dec. 11, 2020	244906	0013, 0034	COVID-19 Interim Order Application	
0037	Dec. 16, 2020	244906	0003	COVID-19 Interim Order Application	
0038	Dec. 17, 2020	244906	0003	COVID-19 Interim Order Application	
0039	Dec. 17, 2020	244906	0003	COVID-19 Interim Order Application	
0040	Dec. 18, 2020	244906	0024	COVID-19 Interim Order Application	
0041	Dec. 18, 2020	244906	0027	COVID-19 Interim Order Application	



Life Cycle Management Table

Sponsor Name: BioNTech Manufacturing GmbH					
Brand Name: PFIZER-BIONTECH COVID-19 VACCINE					
Dossier Identifier: e243022					
Sequence Number	Date Submitted	Control Number	Related Sequence	Regulatory Activity Type	Sequence Description
0042	Dec. 18, 2020	244906	0037	COVID-19 Interim Order Application	
0043	Dec. 21, 2020	244906	0023	COVID-19 Interim Order Application	
0044	Dec. 22, 2020	244906	0003	COVID-19 Interim Order Application	
0045	Jan. 07, 2021	---	---	COVID-19 Interim Order Application - Amendment	
0046	Jan. 07, 2021	248078	---	COVID-19 Interim Order Application - Amendment	
0047	Jan. 08, 2021	---	---	COVID-19 Interim Order Application - Amendment	
0048	Jan. 08, 2021	---	---	COVID-19 Interim Order Application - Amendment	
0049	Jan. 11, 2021	247923	0025	COVID-19 Interim Order Application	



Life Cycle Management Table

Sponsor Name: BioNTech Manufacturing GmbH					
Brand Name: PFIZER-BIONTECH COVID-19 VACCINE					
Dossier Identifier: e243022					
Sequence Number	Date Submitted	Control Number	Related Sequence	Regulatory Activity Type	Sequence Description
0050	Jan. 12, 2021	244906	0003	COVID-19 Interim Order Application	
0051	Jan. 13, 2021	248628, 248272	---	COVID-19 Interim Order Application - Amendment	
0052	Jan. 13, 2021	244906	0003	COVID-19 Interim Order Application	
0053	Jan. 14, 2021	248078	0046	COVID-19 Interim Order Application - Amendment	
0054	Jan. 15, 2021	244906	0025	COVID-19 Interim Order Application	
0055	Jan. 19, 2021	244906	0003	COVID-19 Interim Order Application	
0056	Jan. 20, 2021	244906	0003	COVID-19 Interim Order Application	
0057	Jan. 21, 2021	---	---	COVID-19 Interim Order Application - Amendment	
0058	Jan. 22, 2021	248628, 248272	---	COVID-19 Interim Order Application - Amendment	



Life Cycle Management Table

Sponsor Name: BioNTech Manufacturing GmbH					
Brand Name: PFIZER-BIONTECH COVID-19 VACCINE					
Dossier Identifier: e243022					
Sequence Number	Date Submitted	Control Number	Related Sequence	Regulatory Activity Type	Sequence Description
0059	Jan. 22, 2021	---	---	COVID-19 Interim Order Application - Amendment	
0060	Jan. 26, 2021	247923	0049	COVID-19 Interim Order Application	
0061	Jan. 26, 2021	248628, 248272	0058	COVID-19 Interim Order Application - Amendment	
0062	Feb. 02, 2021	248628	0058	COVID-19 Interim Order Application - Amendment	
0063	Feb. 03, 2021	244906	0003	COVID-19 Interim Order Application	
0064	Feb. 03, 2021	247923	0060	COVID-19 Interim Order Application	
0065	Feb. 05, 2021	248628	0058	COVID-19 Interim Order Application - Amendment	
0066	Feb. 08, 2021	248628	0058	COVID-19 Interim Order Application - Amendment	
0067	Feb. 08, 2021	248628	0058	COVID-19 Interim Order Application - Amendment	



Life Cycle Management Table

Sponsor Name: BioNTech Manufacturing GmbH					
Brand Name: PFIZER-BIONTECH COVID-19 VACCINE					
Dossier Identifier: e243022					
Sequence Number	Date Submitted	Control Number	Related Sequence	Regulatory Activity Type	Sequence Description
0068	Feb. 10, 2021	---	---	COVID-19 Interim Order Application - Amendment	
0069	Feb. 11, 2021	248078	0046	COVID-19 Interim Order Application - Amendment	
0070	Feb. 12, 2021	---	---	COVID-19 Interim Order Application - Amendment	
0071	Feb. 12, 2021	248272, 248628	0051, 0058	COVID-19 Interim Order Application - Amendment	
0072	Feb. 15, 2021	248783	0025,0054	COVID-19 Interim Order Application	
0073	Feb. 16, 2021	248628	0058	COVID-19 Interim Order Application - Amendment	
0074	Feb. 16, 2021	247923	0049, 0060, 0064	COVID-19 Interim Order Application	
0075	Feb. 22, 2021	248628	0058	COVID-19 Interim Order Application - Amendment	
0076	Feb. 25, 2021	249850	---	COVID-19 Interim Order Application - Amendment	



Life Cycle Management Table

Sponsor Name: BioNTech Manufacturing GmbH					
Brand Name: PFIZER-BIONTECH COVID-19 VACCINE					
Dossier Identifier: e243022					
Sequence Number	Date Submitted	Control Number	Related Sequence	Regulatory Activity Type	Sequence Description
0077	Feb. 25, 2021	248272, 248628	0058, 071	COVID-19 Interim Order Application - Amendment	
0078	Mar. 01, 2021	249850	0076	COVID-19 Interim Order Application - Amendment	
0079	Mar. 01, 2021	248628	0058, 0062, 0075	COVID-19 Interim Order Application - Amendment	
0080	Mar. 02, 2021	---	---	COVID-19 Interim Order Application – Amendment	
0081	Mar. 03, 2021	244906	0003	COVID-19 Interim Order Application	
0082	Mar. 03, 2021	249850	0076, 0078	COVID-19 Interim Order Application - Amendment	
0083	Mar. 03, 2021	250082	---	COVID-19 Interim Order Application – Amendment	
0084	Mar. 05, 2021	248628	0058, 0075, 0079	COVID-19 Interim Order Application – Amendment	
0085	Mar. 08, 2021	249850	0082	COVID-19 Interim Order Application – Amendment	



Life Cycle Management Table

Sponsor Name: BioNTech Manufacturing GmbH					
Brand Name: PFIZER-BIONTECH COVID-19 VACCINE					
Dossier Identifier: e243022					
Sequence Number	Date Submitted	Control Number	Related Sequence	Regulatory Activity Type	Sequence Description
0086	Mar. 09, 2021	244906	0003, 0081	COVID-19 Interim Order Application – Amendment	
0087	Mar. 11, 2021	250059	0072	COVID-19 Interim Order Application	
0088	Mar. 12, 2021	249850	0076	COVID-19 Interim Order Application – Amendment	
0089	Mar. 15, 2021	250059	0054, 0072	COVID-19 Interim Order Application	
0090	Mar. 15, 2021	249850	0076, 0088	COVID-19 Interim Order Application – Amendment	
0091	Mar. 16, 2021	250410	---	PA-PV	
0092	Mar. 22, 2021	---	---	COVID-19 Interim Order Application – Amendment	
0093	Mar. 22, 2021	249850	0076, 0088, 0090	COVID-19 Interim Order Application – Amendment	
0094	Mar. 24, 2021	244906	0003, 0044, 0063	COVID-19 Interim Order Application	



Life Cycle Management Table

Sponsor Name: BioNTech Manufacturing GmbH					
Brand Name: PFIZER-BIONTECH COVID-19 VACCINE					
Dossier Identifier: e243022					
Sequence Number	Date Submitted	Control Number	Related Sequence	Regulatory Activity Type	Sequence Description
0095	Apr. 02, 2021	---	---	COVID-19 Interim Order Application – Amendment	
0096	Apr. 02, 2021	---	---	COVID-19 Interim Order Application – Amendment	
0097	Apr. 06, 2021	244906	---	COVID-19 Interim Order Application	
0098	Apr. 13, 2021	250082	0083	COVID-19 Interim Order Application – Amendment	
0099	Apr. 13, 2021	248628	0058	COVID-19 Interim Order Application – Amendment	
0100	Apr. 15, 2021	244906	0054, 0072, and 0089	COVID-19 Interim Order Application	
0101	Apr. 16, 2021	251730	---	COVID-19 Interim Order Application – Amendment	
0102	Apr. 16, 2021	244906	0003, 0044, 0063, 0094	COVID-19 Interim Order Application	
0103	Apr. 16, 2021	251744	---	NDS-CV	



Life Cycle Management Table

Sponsor Name: BioNTech Manufacturing GmbH					
Brand Name: PFIZER-BIONTECH COVID-19 VACCINE					
Dossier Identifier: e243022					
Sequence Number	Date Submitted	Control Number	Related Sequence	Regulatory Activity Type	Sequence Description
0104	Apr. 19, 2021	244906	---	COVID-19 Interim Order Application	
0105	Apr. 21, 2021	---	---	COVID-19 Interim Order Application – Amendment	
0106	Apr. 21, 2021	251730	0101	COVID-19 Interim Order Application – Amendment	
0107	Apr. 27, 2021	252087	---	COVID-19 Interim Order Application – Amendment	
0108	Apr. 28, 2021	251730	0101	COVID-19 Interim Order Application – Amendment	
0109	Apr. 30, 2021	251730	0101	COVID-19 Interim Order Application – Amendment	
0110	May 04, 2021	251730	0101	COVID-19 Interim Order Application – Amendment	
0111	May 04, 2021	251730	0101	COVID-19 Interim Order Application – Amendment	
0112	May 05, 2021	252087	0107	COVID-19 Interim Order Application – Amendment	



Life Cycle Management Table

Sponsor Name: BioNTech Manufacturing GmbH					
Brand Name: PFIZER-BIONTECH COVID-19 VACCINE					
Dossier Identifier: e243022					
Sequence Number	Date Submitted	Control Number	Related Sequence	Regulatory Activity Type	Sequence Description
0113	May 05, 2021	---	---	COVID-19 Interim Order Application – Amendment	
0114	May 05, 2021	251730	0101	COVID-19 Interim Order Application – Amendment	
0115	May 07, 2021	252087	0107	COVID-19 Interim Order Application – Amendment	
0116	May 07, 2021	251813, 251814	0054, 0072, 0089, 0100	COVID-19 Interim Order Application	
0117	May 10, 2021	---	---	COVID-19 Interim Order Application – Amendment	
0118	May 11, 2021	---	--	COVID-19 Interim Order Application	
0119	May 12, 2021	---	---	COVID-19 Interim Order Application – Amendment	
0120	May 12, 2021	251744	0103	NDS-CV	
0121	May 12, 2021	252087	0107	COVID-19 Interim Order Application – Amendment	



Life Cycle Management Table

Sponsor Name: BioNTech Manufacturing GmbH					
Brand Name: PFIZER-BIONTECH COVID-19 VACCINE					
Dossier Identifier: e243022					
Sequence Number	Date Submitted	Control Number	Related Sequence	Regulatory Activity Type	Sequence Description
0122	May 14, 2021	251813	0054, 0072, 0089, 0100	COVID-19 Interim Order Application	
0123	May 17, 2021	252524	0117	COVID-19 Interim Order Application – Amendment	
0124	May 18, 2021	252524	0117	COVID-19 Interim Order Application – Amendment	
0125	May 20, 2021	---	---	COVID-19 Interim Order Application – Amendment	
0126	May 20, 2021	251813, 252392	100, 116, 0122	COVID-19 Interim Order Application	
0127	May 24, 2021	251730	0101, 0111	COVID-19 Interim Order Application – Amendment	
0128	May 28, 2021	252524	0117	COVID-19 Interim Order Application – Amendment	
0129	May 28, 2021	---	---	COVID-19 Interim Order Application – Amendment	
0130	Jun. 02, 2021	---	---	MPNDS	



Life Cycle Management Table

Sponsor Name: BioNTech Manufacturing GmbH					
Brand Name: PFIZER-BIONTECH COVID-19 VACCINE					
Dossier Identifier: e243022					
Sequence Number	Date Submitted	Control Number	Related Sequence	Regulatory Activity Type	Sequence Description
0131	Jun. 03, 2021	---	---	COVID-19 Interim Order Application – Amendment	
0132	Jun. 03, 2021	252087	0107	COVID-19 Interim Order Application – Amendment	
0133	Jun. 14, 2021	253419	0054, 0072, 0089, 0100, 0116, 0122	COVID-19 Interim Order Application	

Regulatory Transaction Template: Regulatory Enrolment Process (REP) (Version: 4.2.4)

Company Identifier	Dossier Type	Dossier Identifier	Date Last Saved
18179	Biologic	e243022	2021-06-14

Regulatory Information

Product Name: PFIZER-BIONTECH COVID-19 VACCINE

Was this regulatory activity approved for priority review? No

Was this regulatory activity approved for NOC/C review? No

Is this regulatory activity an Administrative Submission or does this regulatory activity contain an administrative component? No

Transaction Details

Transaction Details Record

Control Number: 253419

Regulatory Activity Lead: Biological

Regulatory Activity Lead Description:

Biological: Includes all regulatory activities and transactions under the Biologics and Radiopharmaceutical Drugs Directorate (BRDD) mandate (biologics/radiopharmaceuticals).

Regulatory Activity Type: COV19 (COVID-19 Interim Order Application)

Regulatory Transaction Description: Response to E-mail Request dated 2021-06-07

Requester of solicited information:

Requester 1: Melissa Hunt

Are new or revised fees associated with this transaction? Please identify fees when applying for remission. No

Contact for THIS Regulatory Activity

Regulatory Activity Contact for THIS transaction

A. Company Information:

Is the contact for this regulatory activity a third party corresponding on behalf of the manufacturer/sponsor? Yes

- If the regulatory activity type is COV19, COV19A, NDS, SNDS, ANDS, SANDS, SNDS-C, SANDS-C, NC, EUNDS, EUSNDS, EUANDS, EUSANDS, DINA, DINB, DIND, DINF, PDC, PDC-B, then a Third Party Authorization letter is required within the initial transaction of the regulatory activity.
- If the contact changed, a new letter of authorization is required.
- If the contact did not change, another third party authorization letter is not required under the same control#.

Company Name (Full Legal Name)

Pfizer Canada ULC

B. Address Information:

17300 Trans-Canada Highway
Kirkland, Quebec, Canada
H9J 2M5

C. Company Representative:**Job Title** [REDACTED] Regulatory**Language of Correspondence** English

Affairs

First Name [REDACTED]**Initials****Last Name** [REDACTED]**Phone Number** [REDACTED] **Ext****Fax Number** 5144266824**Email** eSubmissions-CA@pfizer.com**Routing Identifier**☒ I confirm that the above regulatory activity contact information is valid.

FACT SHEET FOR RECIPIENTS AND CAREGIVERS

EMERGENCY USE AUTHORIZATION (EUA) OF THE PFIZER-BIONTECH COVID-19 VACCINE TO PREVENT CORONAVIRUS DISEASE 2019 (COVID-19) IN INDIVIDUALS 12 YEARS OF AGE AND OLDER

You are being offered the Pfizer-BioNTech COVID-19 Vaccine to prevent Coronavirus Disease 2019 (COVID-19) caused by SARS-CoV-2. This Fact Sheet contains information to help you understand the risks and benefits of the Pfizer-BioNTech COVID-19 Vaccine, which you may receive because there is currently a pandemic of COVID-19.

The Pfizer-BioNTech COVID-19 Vaccine is a vaccine and may prevent you from getting COVID-19. There is no U.S. Food and Drug Administration (FDA) approved vaccine to prevent COVID-19.

Read this Fact Sheet for information about the Pfizer-BioNTech COVID-19 Vaccine. Talk to the vaccination provider if you have questions. It is your choice to receive the Pfizer-BioNTech COVID-19 Vaccine.

The Pfizer-BioNTech COVID-19 Vaccine is administered as a 2-dose series, 3 weeks apart, into the muscle.

The Pfizer-BioNTech COVID-19 Vaccine may not protect everyone.

This Fact Sheet may have been updated. For the most recent Fact Sheet, please see www.cvdvaccine.com.

WHAT YOU NEED TO KNOW BEFORE YOU GET THIS VACCINE

WHAT IS COVID-19?

COVID-19 disease is caused by a coronavirus called SARS-CoV-2. This type of coronavirus has not been seen before. You can get COVID-19 through contact with another person who has the virus. It is predominantly a respiratory illness that can affect other organs. People with COVID-19 have had a wide range of symptoms reported, ranging from mild symptoms to severe illness. Symptoms may appear 2 to 14 days after exposure to the virus. Symptoms may include: fever or chills; cough; shortness of breath; fatigue; muscle or body aches; headache; new loss of taste or smell; sore throat; congestion or runny nose; nausea or vomiting; diarrhea.

WHAT IS THE PFIZER-BIONTECH COVID-19 VACCINE?

The Pfizer-BioNTech COVID-19 Vaccine is an unapproved vaccine that may prevent COVID-19. There is no FDA-approved vaccine to prevent COVID-19.

The FDA has authorized the emergency use of the Pfizer-BioNTech COVID-19 Vaccine to prevent COVID-19 in individuals 12 years of age and older under an Emergency Use Authorization (EUA).

For more information on EUA, see the “**What is an Emergency Use Authorization (EUA)?**” section at the end of this Fact Sheet.

WHAT SHOULD YOU MENTION TO YOUR VACCINATION PROVIDER BEFORE YOU GET THE PFIZER-BIONTECH COVID-19 VACCINE?

Tell the vaccination provider about all of your medical conditions, including if you:

- have any allergies
- have had myocarditis (inflammation of the heart muscle) or pericarditis (inflammation of the lining outside the heart)
- have a fever
- have a bleeding disorder or are on a blood thinner
- are immunocompromised or are on a medicine that affects your immune system
- are pregnant or plan to become pregnant
- are breastfeeding
- have received another COVID-19 vaccine
- have ever fainted in association with an injection

WHO SHOULD GET THE PFIZER-BIONTECH COVID-19 VACCINE?

FDA has authorized the emergency use of the Pfizer-BioNTech COVID-19 Vaccine in individuals 12 years of age and older.

WHO SHOULD NOT GET THE PFIZER-BIONTECH COVID-19 VACCINE?

You should not get the Pfizer-BioNTech COVID-19 Vaccine if you:

- had a severe allergic reaction after a previous dose of this vaccine
- had a severe allergic reaction to any ingredient of this vaccine.

WHAT ARE THE INGREDIENTS IN THE PFIZER-BIONTECH COVID-19 VACCINE?

The Pfizer-BioNTech COVID-19 Vaccine includes the following ingredients: mRNA, lipids ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), 2 [(polyethylene glycol)-2000]-N,N-ditetradecylacetamide, 1,2-Distearoyl-sn-glycero-3-phosphocholine, and cholesterol), potassium chloride, monobasic potassium phosphate, sodium chloride, dibasic sodium phosphate dihydrate, and sucrose.

HOW IS THE PFIZER-BIONTECH COVID-19 VACCINE GIVEN?

The Pfizer-BioNTech COVID-19 Vaccine will be given to you as an injection into the muscle.

The Pfizer-BioNTech COVID-19 Vaccine vaccination series is 2 doses given 3 weeks apart.

If you receive one dose of the Pfizer-BioNTech COVID-19 Vaccine, you should receive a second dose of this same vaccine 3 weeks later to complete the vaccination series.

HAS THE PFIZER-BIONTECH COVID-19 VACCINE BEEN USED BEFORE?

The Pfizer-BioNTech COVID-19 Vaccine is an unapproved vaccine. In clinical trials, approximately 23,000 individuals 12 years of age and older have received at least 1 dose of the Pfizer-BioNTech COVID-19 Vaccine.

WHAT ARE THE BENEFITS OF THE PFIZER-BIONTECH COVID-19 VACCINE?

In an ongoing clinical trial, the Pfizer-BioNTech COVID-19 Vaccine has been shown to prevent COVID-19 following 2 doses given 3 weeks apart. The duration of protection against COVID-19 is currently unknown.

WHAT ARE THE RISKS OF THE PFIZER-BIONTECH COVID-19 VACCINE?

There is a remote chance that the Pfizer-BioNTech COVID-19 Vaccine could cause a severe allergic reaction. A severe allergic reaction would usually occur within a few minutes to one hour after getting a dose of the Pfizer-BioNTech COVID-19 Vaccine. For this reason, your vaccination provider may ask you to stay at the place where you received your vaccine for monitoring after vaccination. Signs of a severe allergic reaction can include:

- Difficulty breathing
- Swelling of your face and throat
- A fast heartbeat
- A bad rash all over your body
- Dizziness and weakness

Myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) have occasionally occurred in people who have received the Pfizer-BioNTech COVID-19 Vaccine. In most of these people, symptoms began within a few days following receipt of the second dose of the Pfizer-BioNTech COVID-19 Vaccine. The chance of having this occur is very low. You should seek medical attention right away if you have any of the following symptoms after receiving the Pfizer-BioNTech COVID-19 Vaccine:

- Chest pain
- Shortness of breath
- Feelings of having a fast-beating, fluttering, or pounding heart.

Side effects that have been reported with the Pfizer-BioNTech COVID-19 Vaccine include:

- severe allergic reactions
- non-severe allergic reactions such as rash, itching, hives, or swelling of the face
- myocarditis (inflammation of the heart muscle)
- pericarditis (inflammation of the lining outside the heart)
- injection site pain
- tiredness
- headache
- muscle pain
- chills
- joint pain
- fever
- injection site swelling

- injection site redness
- nausea
- feeling unwell
- swollen lymph nodes (lymphadenopathy)
- diarrhea
- vomiting
- arm pain

These may not be all the possible side effects of the Pfizer-BioNTech COVID-19 Vaccine. Serious and unexpected side effects may occur. Pfizer-BioNTech COVID-19 Vaccine is still being studied in clinical trials.

WHAT SHOULD I DO ABOUT SIDE EFFECTS?

If you experience a severe allergic reaction, call 9-1-1, or go to the nearest hospital.

Call the vaccination provider or your healthcare provider if you have any side effects that bother you or do not go away.

Report vaccine side effects to FDA/CDC Vaccine Adverse Event Reporting System (VAERS). The VAERS toll-free number is 1-800-822-7967 or report online to <https://vaers.hhs.gov/reportevent.html>. Please include "Pfizer-BioNTech COVID-19 Vaccine EUA" in the first line of box #18 of the report form.

In addition, you can report side effects to Pfizer Inc. at the contact information provided below.

Website	Fax number	Telephone number
www.pfizersafetyreporting.com	1-866-635-8337	1-800-438-1985

You may also be given an option to enroll in v-safe. V-safe is a new voluntary smartphone-based tool that uses text messaging and web surveys to check in with people who have been vaccinated to identify potential side effects after COVID-19 vaccination. V-safe asks questions that help CDC monitor the safety of COVID-19 vaccines. V-safe also provides second-dose reminders if needed and live telephone follow-up by CDC if participants report a significant health impact following COVID-19 vaccination. For more information on how to sign up, visit: www.cdc.gov/vsafe.

WHAT IF I DECIDE NOT TO GET THE PFIZER-BIONTECH COVID-19 VACCINE?

It is your choice to receive or not receive the Pfizer-BioNTech COVID-19 Vaccine. Should you decide not to receive it, it will not change your standard medical care.

ARE OTHER CHOICES AVAILABLE FOR PREVENTING COVID-19 BESIDES PFIZER-BIONTECH COVID-19 VACCINE?

Currently, there is no approved alternative vaccine available for prevention of COVID-19. Other vaccines to prevent COVID-19 may be available under Emergency Use Authorization.

CAN I RECEIVE THE PFIZER-BIONTECH COVID-19 VACCINE WITH OTHER VACCINES?

There is no information on the use of the Pfizer-BioNTech COVID-19 Vaccine with other vaccines.

WHAT IF I AM PREGNANT OR BREASTFEEDING?

If you are pregnant or breastfeeding, discuss your options with your healthcare provider.

WILL THE PFIZER-BIONTECH COVID-19 VACCINE GIVE ME COVID-19?

No. The Pfizer-BioNTech COVID-19 Vaccine does not contain SARS-CoV-2 and cannot give you COVID-19.


KEEP YOUR VACCINATION CARD

When you get your first dose, you will get a vaccination card to show you when to return for your second dose of Pfizer-BioNTech COVID-19 Vaccine. Remember to bring your card when you return.

ADDITIONAL INFORMATION

If you have questions, visit the website or call the telephone number provided below.

To access the most recent Fact Sheets, please scan the QR code provided below.

Global website	Telephone number
www.cvdvaccine.com 	1-877-829-2619 (1-877-VAX-CO19)

HOW CAN I LEARN MORE?

- Ask the vaccination provider.
- Visit CDC at <https://www.cdc.gov/coronavirus/2019-ncov/index.html>.
- Visit FDA at <https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization>.
- Contact your local or state public health department.

WHERE WILL MY VACCINATION INFORMATION BE RECORDED?

The vaccination provider may include your vaccination information in your state/local jurisdiction's Immunization Information System (IIS) or other designated system. This will ensure that you receive the same vaccine when you return for the second dose. For more information about IISs visit: <https://www.cdc.gov/vaccines/programs/iis/about.html>.

CAN I BE CHARGED AN ADMINISTRATION FEE FOR RECEIPT OF THE COVID-19 VACCINE?

No. At this time, the provider cannot charge you for a vaccine dose and you cannot be charged an out-of-pocket vaccine administration fee or any other fee if only receiving a COVID-19 vaccination. However, vaccination providers may seek appropriate reimbursement from a program or plan that covers COVID-19 vaccine administration fees for the vaccine recipient (private insurance, Medicare, Medicaid, Health Resources & Services Administration [HRSA] COVID-19 Uninsured Program for non-insured recipients).

WHERE CAN I REPORT CASES OF SUSPECTED FRAUD?

Individuals becoming aware of any potential violations of the CDC COVID-19 Vaccination Program requirements are encouraged to report them to the Office of the Inspector General, U.S. Department of Health and Human Services, at 1-800-HHS-TIPS or <https://TIPS.HHS.GOV>.

WHAT IS THE COUNTERMEASURES INJURY COMPENSATION PROGRAM?

The Countermeasures Injury Compensation Program (CICP) is a federal program that may help pay for costs of medical care and other specific expenses of certain people who have been seriously injured by certain medicines or vaccines, including this vaccine. Generally, a claim must be submitted to the CICP within one (1) year from the date of receiving the vaccine. To learn more about this program, visit www.hrsa.gov/cicp/ or call 1-855-266-2427.

WHAT IS AN EMERGENCY USE AUTHORIZATION (EUA)?

The United States FDA has made the Pfizer-BioNTech COVID-19 Vaccine available under an emergency access mechanism called an EUA. The EUA is supported by a Secretary of Health and Human Services (HHS) declaration that circumstances exist to justify the emergency use of drugs and biological products during the COVID-19 pandemic.

The Pfizer-BioNTech COVID-19 Vaccine has not undergone the same type of review as an FDA-approved or cleared product. FDA may issue an EUA when certain criteria are met, which includes that there are no adequate, approved, available alternatives. In addition, the FDA decision is based on the totality of scientific evidence available showing that the product may be effective to prevent COVID-19 during the COVID-19 pandemic and that the known and potential benefits of the product outweigh the known and potential risks of the product. All of these criteria must be met to allow for the product to be used in the treatment of patients during the COVID-19 pandemic.

The EUA for the Pfizer-BioNTech COVID-19 Vaccine is in effect for the duration of the COVID-19 EUA declaration justifying emergency use of these products, unless terminated or revoked (after which the products may no longer be used).



Manufactured by
Pfizer Inc., New York, NY 10017

BIONTECH

Manufactured for
BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz, Germany

LAB-1451-4.2a

Revised: ~~10 Mayxx~~ June 2021



Scan to capture that this Fact Sheet was provided to vaccine
recipient for the electronic medical records/immunization
information systems.

Barcode Date: 05/2021

FACT SHEET FOR HEALTHCARE PROVIDERS ADMINISTERING VACCINE (VACCINATION PROVIDERS)

EMERGENCY USE AUTHORIZATION (EUA) OF THE PFIZER-BIONTECH COVID-19 VACCINE TO PREVENT CORONAVIRUS DISEASE 2019 (COVID-19)

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved product, **Pfizer-BioNTech COVID-19 Vaccine**, for active immunization to prevent COVID-19 in individuals 12 years of age and older.

SUMMARY OF INSTRUCTIONS FOR COVID-19 VACCINATION PROVIDERS

Vaccination providers enrolled in the federal COVID-19 Vaccination Program must report all vaccine administration errors, all serious adverse events, cases of Multisystem Inflammatory Syndrome (MIS) in adults and children, and cases of COVID-19 that result in hospitalization or death following administration of Pfizer-BioNTech COVID-19 Vaccine. See “MANDATORY REQUIREMENTS FOR PFIZER-BIONTECH COVID-19 VACCINE ADMINISTRATION UNDER EMERGENCY USE AUTHORIZATION” for reporting requirements.

The Pfizer-BioNTech COVID-19 Vaccine is a suspension for intramuscular injection administered as a series of two doses (0.3 mL each) 3 weeks apart.

See this Fact Sheet for instructions for preparation and administration. This Fact Sheet may have been updated. For the most recent Fact Sheet, please see www.cvdvaccine.com.

For information on clinical trials that are testing the use of the Pfizer-BioNTech COVID-19 Vaccine for active immunization against COVID-19, please see www.clinicaltrials.gov.

DESCRIPTION OF COVID-19

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by the novel coronavirus, SARS-CoV-2, that appeared in late 2019. It is predominantly a respiratory illness that can affect other organs. People with COVID-19 have reported a wide range of symptoms, ranging from mild symptoms to severe illness. Symptoms may appear 2 to 14 days after exposure to the virus. Symptoms may include: fever or chills; cough; shortness of breath; fatigue; muscle or body aches; headache; new loss of taste or smell; sore throat; congestion or runny nose; nausea or vomiting; diarrhea.

DOSAGE AND ADMINISTRATION

Storage and Handling

During storage, minimize exposure to room light, and avoid exposure to direct sunlight and ultraviolet light.

Do not refreeze thawed vials.

Frozen Vials Prior to Use

Cartons of Pfizer-BioNTech COVID-19 Vaccine Multiple Dose Vials arrive in thermal containers with dry ice. Once received, remove the vial cartons immediately from the thermal container and preferably store in an ultra-low temperature freezer between -80°C to -60°C (-112°F to -76°F) until the expiry date printed on the label. Alternatively, vials may be stored at -25°C to -15°C (-13°F to 5°F) for up to 2 weeks. Vials must be kept frozen and protected from light until ready to use. Vials stored at -25°C to -15°C (-13°F to 5°F) for up to 2 weeks may be returned one time to the recommended storage condition of -80°C to -60°C (-112°F to -76°F). Total cumulative time the vials are stored at -25°C to -15°C (-13°F to 5°F) should be tracked and should not exceed 2 weeks.

If an ultra-low temperature freezer is not available, the thermal container in which the Pfizer-BioNTech COVID-19 Vaccine arrives may be used as temporary storage when consistently re-filled to the top of the container with dry ice. Refer to the re-icing guidelines packed in the original thermal container for instructions regarding the use of the thermal container for temporary storage. The thermal container maintains a temperature range of -90°C to -60°C (-130°F to -76°F). Storage of the vials between -96°C to -60°C (-141°F to -76°F) is not considered an excursion from the recommended storage condition.

Transportation of Frozen Vials

If local redistribution is needed and full cartons containing vials cannot be transported at -90°C to -60°C (-130°F to -76°F), vials may be transported at -25°C to -15°C (-13°F to 5°F). Any hours used for transport at -25°C to -15°C (-13°F to 5°F) count against the 2-week limit for storage at -25°C to -15°C (-13°F to 5°F). Frozen vials transported at -25°C to -15°C (-13°F to 5°F) may be returned one time to the recommended storage condition of -80°C to -60°C (-112°F to -76°F).

Thawed Vials Before Dilution

Thawed Under Refrigeration

Thaw and then store undiluted vials in the refrigerator [2°C to 8°C (35°F to 46°F)] for up to 1 month. A carton of 25 vials or 195 vials may take up to 2 or 3 hours, respectively, to thaw in the refrigerator, whereas a fewer number of vials will thaw in less time.

Thawed at Room Temperature

For immediate use, thaw undiluted vials at room temperature [up to 25°C (77°F)] for 30 minutes. Thawed vials can be handled in room light conditions. Vials must reach room temperature before dilution.

Undiluted vials may be stored at room temperature for no more than 2 hours.

Transportation of Thawed Vials

Available data support transportation of one or more thawed vials at 2°C to 8°C (35°F to 46°F) for up to 12 hours.

Vials After Dilution

- After dilution, store vials between 2°C to 25°C (35°F to 77°F) and use within 6 hours from the time of dilution.
- During storage, minimize exposure to room light, and avoid exposure to direct sunlight and ultraviolet light.
- Any vaccine remaining in vials must be discarded after 6 hours.
- Do not refreeze.

Dosing and Schedule

The Pfizer-BioNTech COVID-19 Vaccine is administered intramuscularly as a series of two doses (0.3 mL each) 3 weeks apart.

There are no data available on the interchangeability of the Pfizer-BioNTech COVID-19 Vaccine with other COVID-19 vaccines to complete the vaccination series. Individuals who have received one dose of Pfizer-BioNTech COVID-19 Vaccine should receive a second dose of Pfizer-BioNTech COVID-19 Vaccine to complete the vaccination series.

Dose Preparation

Prior to Dilution

- The Pfizer-BioNTech COVID-19 Vaccine Multiple Dose Vial contains a volume of 0.45 mL, supplied as a frozen suspension that does not contain preservative. Each vial must be thawed and diluted prior to administration.
- Vials may be thawed in the refrigerator [2°C to 8°C (35°F to 46°F)] or at room temperature [up to 25°C (77°F)] (*see Storage and Handling*).
- Refer to thawing instructions in the panels below.

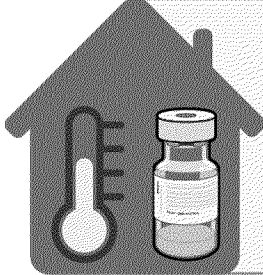
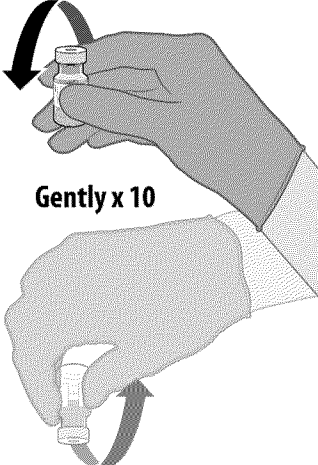
Dilution

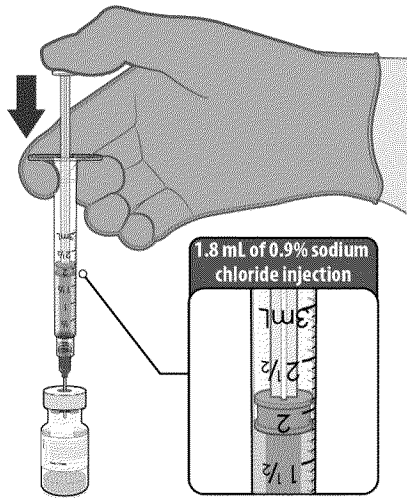
Dilute the vial contents using 1.8 mL of 0.9% Sodium Chloride Injection, USP (not provided) to form the Pfizer-BioNTech COVID-19 Vaccine. ONLY use 0.9% Sodium Chloride Injection, USP as the diluent. This diluent is not packaged with the vaccine

and must be sourced separately. Do not use bacteriostatic 0.9% Sodium Chloride Injection or any other diluent. Do not add more than 1.8 mL of diluent.

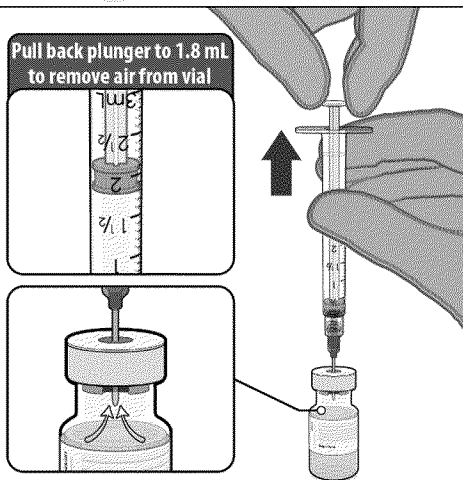
After dilution, one vial contains 6 doses of 0.3 mL. Vial labels and cartons may state that after dilution, a vial contains 5 doses of 0.3 mL. The information in this Fact Sheet regarding the number of doses per vial after dilution supersedes the number of doses stated on vial labels and cartons.

- Refer to dilution and dose preparation instructions in the panels below.

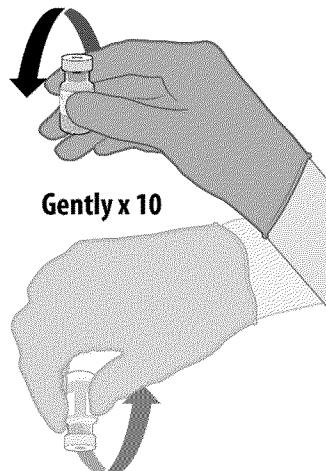
THAWING PRIOR TO DILUTION	
 <p>No more than 2 hours at room temperature (up to 25°C / 77°F)</p>	<ul style="list-style-type: none"> • Thaw vial(s) of Pfizer-BioNTech COVID-19 Vaccine before use either by: <ul style="list-style-type: none"> ○ Allowing vial(s) to thaw in the refrigerator [2°C to 8°C (35°F to 46°F)]. A carton of vials may take up to 3 hours to thaw, and thawed vials can be stored in the refrigerator for up to 1 month. ○ Allowing vial(s) to sit at room temperature [up to 25°C (77°F)] for 30 minutes. • Using either thawing method, vials must reach room temperature before dilution and must be diluted within 2 hours.
 <p>Gently x 10</p>	<ul style="list-style-type: none"> • Before dilution invert vaccine vial gently 10 times. • <u>Do not shake.</u> • Inspect the liquid in the vial prior to dilution. The liquid is a white to off-white suspension and may contain white to off-white opaque amorphous particles. • Do not use if liquid is discolored or if other particles are observed.

DILUTION

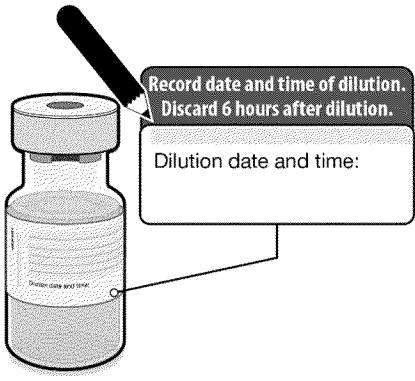
- Obtain sterile 0.9% Sodium Chloride Injection, USP. Use only this as the diluent.
- Using aseptic technique, withdraw 1.8 mL of diluent into a transfer syringe (21-gauge or narrower needle).
- Cleanse the vaccine vial stopper with a single-use antiseptic swab.
- Add 1.8 mL of 0.9% Sodium Chloride Injection, USP into the vaccine vial.



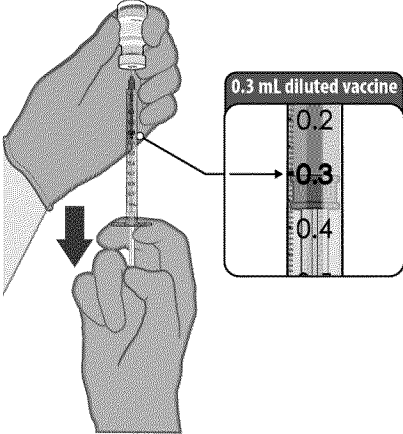
- Equalize vial pressure before removing the needle from the vial by withdrawing 1.8 mL air into the empty diluent syringe.



- Gently invert the vial containing the Pfizer-BioNTech COVID-19 Vaccine 10 times to mix.
- Do not shake.
- Inspect the vaccine in the vial.
- The vaccine will be an off-white suspension. Do not use if vaccine is discolored or contains particulate matter.

 <p>Record date and time of dilution. Discard 6 hours after dilution.</p> <p>Dilution date and time:</p>	<ul style="list-style-type: none"> Record the date and time of dilution on the Pfizer-BioNTech COVID-19 Vaccine vial label. Store between 2°C to 25°C (35°F to 77°F). Discard any unused vaccine 6 hours after dilution.
---	---

PREPARATION OF INDIVIDUAL 0.3 mL DOSES OF PFIZER-BIONTECH COVID-19 VACCINE

 <p>0.3 mL diluted vaccine</p>	<ul style="list-style-type: none"> Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab, and withdraw 0.3 mL of the Pfizer-BioNTech COVID-19 Vaccine preferentially using a low dead-volume syringe and/or needle. Each dose must contain 0.3 mL of vaccine. If the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume. Administer immediately.
--	--

Administration

Visually inspect each dose in the dosing syringe prior to administration. The vaccine will be an off-white suspension. During the visual inspection,

- verify the final dosing volume of 0.3 mL.
- confirm there are no particulates and that no discoloration is observed.
- do not administer if vaccine is discolored or contains particulate matter.

Administer the Pfizer-BioNTech COVID-19 Vaccine intramuscularly.

After dilution, vials of Pfizer-BioNTech COVID-19 Vaccine contain six doses of 0.3 mL of vaccine. Low dead-volume syringes and/or needles can be used to extract six doses from a single vial. If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial. Irrespective of the type of syringe and needle:

- Each dose must contain 0.3 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and content.
- Do not pool excess vaccine from multiple vials.

Contraindications

Do not administer Pfizer-BioNTech COVID-19 Vaccine to individuals with known history of a severe allergic reaction (e.g., anaphylaxis) to any component of the Pfizer-BioNTech COVID-19 Vaccine (see *Full EUA Prescribing Information*).

Warnings

Management of Acute Allergic Reactions

Appropriate medical treatment used to manage immediate allergic reactions must be immediately available in the event an acute anaphylactic reaction occurs following administration of Pfizer-BioNTech COVID-19 Vaccine.

Monitor Pfizer-BioNTech COVID-19 Vaccine recipients for the occurrence of immediate adverse reactions according to the Centers for Disease Control and Prevention (CDC) guidelines (<https://www.cdc.gov/vaccines/covid-19/clinical-considerations/managing-anaphylaxis.html>).

Myocarditis and Pericarditis

Reports of adverse events following use of the Pfizer-BioNTech COVID-19 Vaccine under EUA suggest increased risks of myocarditis and pericarditis, particularly following the second dose. Typically, onset of symptoms has been within a few days following receipt of the Pfizer-BioNTech COVID-19 Vaccine. Available data from short-term follow-up suggest that most individuals have had resolution of symptoms, but information is not yet available about potential long-term sequelae. The decision to administer the Pfizer-BioNTech COVID-19 Vaccine to an individual with a history of myocarditis or pericarditis should take into account the individual's clinical circumstances. The CDC has published clinical considerations relevant to myocarditis and pericarditis associated with administration of the Pfizer-BioNTech COVID-19 Vaccine (<https://www.cdc.gov/vaccines/covid-19/clinical-considerations/myocarditis.html>).

Syncope

Syncope (fainting) may occur in association with administration of injectable vaccines, in particular in adolescents. Procedures should be in place to avoid injury from fainting.

Altered Immunocompetence

Immunocompromised persons, including individuals receiving immunosuppressant therapy, may have a diminished immune response to the Pfizer-BioNTech COVID-19 Vaccine.

Limitation of Effectiveness

Pfizer-BioNTech COVID-19 Vaccine may not protect all vaccine recipients.

Adverse Reactions

Adverse Reactions in Clinical Trials

Adverse reactions following the Pfizer-BioNTech COVID-19 Vaccine that have been reported in clinical trials include injection site pain, fatigue, headache, muscle pain, chills, joint pain, fever, injection site swelling, injection site redness, nausea, malaise, and lymphadenopathy (see *Full EUA Prescribing Information*).

Adverse Reactions in Post Authorization Experience

Severe allergic reactions, including anaphylaxis, and other hypersensitivity reactions (e.g., rash, pruritus, urticaria, angioedema), diarrhea, vomiting, and pain in extremity (arm) have been reported following administration of the Pfizer-BioNTech COVID-19 Vaccine outside of clinical trials.

Additional adverse reactions, some of which may be serious, may become apparent with more widespread use of the Pfizer-BioNTech COVID-19 Vaccine.

Use with Other Vaccines

There is no information on the co-administration of the Pfizer-BioNTech COVID-19 Vaccine with other vaccines.

INFORMATION TO PROVIDE TO VACCINE RECIPIENTS/CAREGIVERS

As the vaccination provider, you must communicate to the recipient or their caregiver, information consistent with the “Fact Sheet for Recipients and Caregivers” (and provide a copy or direct the individual to the website www.cvdvaccine.com to obtain the Fact Sheet) prior to the individual receiving each dose of Pfizer-BioNTech COVID-19 Vaccine, including:

- FDA has authorized the emergency use of the Pfizer-BioNTech COVID-19 Vaccine, which is not an FDA-approved vaccine.
- The recipient or their caregiver has the option to accept or refuse Pfizer-BioNTech COVID-19 Vaccine.
- The significant known and potential risks and benefits of Pfizer-BioNTech COVID-19 Vaccine, and the extent to which such risks and benefits are unknown.
- Information about available alternative vaccines and the risks and benefits of those alternatives.

For information on clinical trials that are testing the use of the Pfizer-BioNTech COVID-19 Vaccine to prevent COVID-19, please see www.clinicaltrials.gov.

Provide a vaccination card to the recipient or their caregiver with the date when the recipient needs to return for the second dose of Pfizer-BioNTech COVID-19 Vaccine.

Provide the v-safe information sheet to vaccine recipients/caregivers and encourage vaccine recipients to participate in v-safe. V-safe is a new voluntary smartphone-based tool that uses text messaging and web surveys to check in with people who have been vaccinated to identify potential side effects after COVID-19 vaccination. V-safe asks questions that help CDC monitor the safety of COVID-19 vaccines. V-safe also provides second-dose reminders if needed and live telephone follow-up by CDC if participants report a significant health impact following COVID-19 vaccination. For more information, visit: www.cdc.gov/vsafe.

MANDATORY REQUIREMENTS FOR PFIZER-BIONTECH COVID-19 VACCINE ADMINISTRATION UNDER EMERGENCY USE AUTHORIZATION

In order to mitigate the risks of using this unapproved product under EUA and to optimize the potential benefit of Pfizer-BioNTech COVID-19 Vaccine, the following items are required. Use of unapproved Pfizer-BioNTech COVID-19 Vaccine for active immunization to prevent COVID-19 under this EUA is limited to the following (all requirements **must** be met):

1. Pfizer-BioNTech COVID-19 Vaccine is authorized for use in individuals 12 years of age and older.
2. The vaccination provider must communicate to the individual receiving the Pfizer-BioNTech COVID-19 Vaccine or their caregiver, information consistent with the “Fact Sheet for Recipients and Caregivers” prior to the individual receiving Pfizer-BioNTech COVID-19 Vaccine.
3. The vaccination provider must include vaccination information in the state/local jurisdiction’s Immunization Information System (IIS) or other designated system.
4. The vaccination provider is responsible for mandatory reporting of the following to the Vaccine Adverse Event Reporting System (VAERS):
 - vaccine administration errors whether or not associated with an adverse event,
 - serious adverse events* (irrespective of attribution to vaccination),
 - cases of Multisystem Inflammatory Syndrome (MIS) in adults and children, and
 - cases of COVID-19 that result in hospitalization or death.

Complete and submit reports to VAERS online at <https://vaers.hhs.gov/reportevent.html>. For further assistance with reporting to VAERS call 1-800-822-7967. The reports should include the words “Pfizer-BioNTech COVID-19 Vaccine EUA” in the description section of the report.

5. The vaccination provider is responsible for responding to FDA requests for information about vaccine administration errors, adverse events, cases of MIS in adults and children, and cases of COVID-19 that result in hospitalization or death following administration of Pfizer-BioNTech COVID-19 Vaccine to recipients.

* Serious adverse events are defined as:

- Death;
- A life-threatening adverse event;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- A congenital anomaly/birth defect;
- An important medical event that based on appropriate medical judgement may jeopardize the individual and may require medical or surgical intervention to prevent one of the outcomes listed above.

OTHER ADVERSE EVENT REPORTING TO VAERS AND PFIZER INC.

Vaccination providers may report to VAERS other adverse events that are not required to be reported using the contact information above.


To the extent feasible, report adverse events to Pfizer Inc. using the contact information below or by providing a copy of the VAERS form to Pfizer Inc.

Website	Fax number	Telephone number
www.pfizersafetyreporting.com	1-866-635-8337	1-800-438-1985

ADDITIONAL INFORMATION

For general questions, visit the website or call the telephone number provided below.

To access the most recent Pfizer-BioNTech COVID-19 Vaccine Fact Sheets, please scan the QR code provided below.

Global website	Telephone number
www.cvdvaccine.com 	1-877-829-2619 (1-877-VAX-CO19)

AVAILABLE ALTERNATIVES

There is no approved alternative vaccine to prevent COVID-19. There may be clinical trials or availability under EUA of other COVID-19 vaccines.

FEDERAL COVID-19 VACCINATION PROGRAM

This vaccine is being made available for emergency use exclusively through the CDC COVID-19 Vaccination Program (the Vaccination Program). Healthcare providers must enroll as providers in the Vaccination Program and comply with the provider requirements. Vaccination providers may not charge any fee for the vaccine and may not charge the vaccine recipient any out-of-pocket charge for administration. However, vaccination providers may seek appropriate reimbursement from a program or plan that covers COVID-19 vaccine administration fees for the vaccine recipient (private insurance, Medicare, Medicaid, Health Resources & Services Administration [HRSA] COVID-19 Uninsured Program for non-insured recipients). For information regarding provider requirements and enrollment in the CDC COVID-19 Vaccination Program, see <https://www.cdc.gov/vaccines/covid-19/provider-enrollment.html>.

Individuals becoming aware of any potential violations of the CDC COVID-19 Vaccination Program requirements are encouraged to report them to the Office of the Inspector General, U.S. Department of Health and Human Services, at 1-800-HHS-TIPS or <https://TIPS.HHS.GOV>.

AUTHORITY FOR ISSUANCE OF THE EUA

The Secretary of Health and Human Services (HHS) has declared a public health emergency that justifies the emergency use of drugs and biological products during the COVID-19 pandemic. In response, FDA has issued an EUA for the unapproved product, Pfizer-BioNTech COVID-19 Vaccine, for active immunization against COVID-19 in individuals 12 years of age and older.

FDA issued this EUA, based on Pfizer-BioNTech's request and submitted data.

Although limited scientific information is available, based on the totality of the scientific evidence available to date, it is reasonable to believe that the Pfizer-BioNTech COVID-19 Vaccine may be effective for the prevention of COVID-19 in individuals as specified in the *Full EUA Prescribing Information*.

This EUA for the Pfizer-BioNTech COVID-19 Vaccine will end when the Secretary of HHS determines that the circumstances justifying the EUA no longer exist or when there is a change in the approval status of the product such that an EUA is no longer needed.

For additional information about Emergency Use Authorization visit FDA at: <https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization>.

The Countermeasures Injury Compensation Program

The Countermeasures Injury Compensation Program (CICP) is a federal program that has been created to help pay for related costs of medical care and other specific expenses to compensate people injured after use of certain medical countermeasures. Medical countermeasures are specific vaccines, medications, devices, or other items used to prevent, diagnose, or treat the public during a public health emergency or a security threat. For more information about CICP regarding the Pfizer-BioNTech COVID-19 Vaccine used to prevent COVID-19, visit www.hrsa.gov/cicp, email cicp@hrsa.gov, or call: 1-855-266-2427.



Manufactured by
Pfizer Inc., New York, NY 10017

BIONTECH

Manufactured for
BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz, Germany

LAB-1450-8.2b

Revised: ~~19 May~~xx June 2021

END SHORT VERSION FACT SHEET
Long Version (Full EUA Prescribing Information) Begins On Next Page

FULL EMERGENCY USE AUTHORIZATION (EUA) PRESCRIBING INFORMATION

PFIZER-BIONTECH COVID-19 VACCINE

FULL EMERGENCY USE AUTHORIZATION PRESCRIBING INFORMATION: CONTENTS*

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- 2 DOSAGE AND ADMINISTRATION**
 - 2.1 Preparation for Administration
 - 2.2 Administration Information
 - 2.3 Vaccination Schedule for Individuals 12 Years of Age and Older
- 3 DOSAGE FORMS AND STRENGTHS**
- 4 CONTRAINDICATIONS**
- 5 WARNINGS AND PRECAUTIONS**
 - ~~5.1~~ Management of Acute Allergic Reactions
 - ~~5.1.5.2~~ Myocarditis and Pericarditis
 - ~~5.2.5.3~~ Syncope
 - ~~5.3.5.4~~ Altered Immunocompetence
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- 6 OVERALL SAFETY SUMMARY**
 - 6.1 Clinical Trials Experience
 - 6.2 Post Authorization Experience

- 8 REQUIREMENTS AND INSTRUCTIONS FOR REPORTING
ADVERSE EVENTS AND VACCINE ADMINISTRATION
ERRORS**
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EUA**
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 - 18.2 Efficacy in Adolescents 12 Through 15 Years of Age
 - 18.3 Immunogenicity in Adolescents 12 Through 15 Years of Age
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- 20 PATIENT COUNSELING INFORMATION**
- 21 CONTACT INFORMATION**

* Sections or subsections omitted from the full emergency use authorization prescribing information are not listed.

FULL EMERGENCY USE AUTHORIZATION (EUA) PRESCRIBING INFORMATION

1 AUTHORIZED USE

Pfizer-BioNTech COVID-19 Vaccine is authorized for use under an Emergency Use Authorization (EUA) for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 12 years of age and older.

2 DOSAGE AND ADMINISTRATION

For intramuscular injection only.

2.1 Preparation for Administration

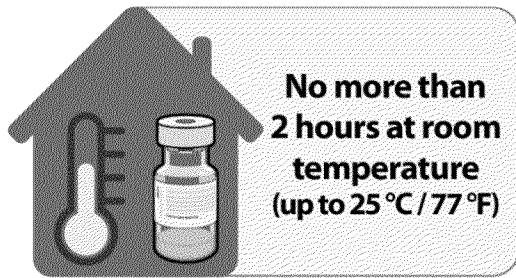
Prior to Dilution

- The Pfizer-BioNTech COVID-19 Vaccine Multiple Dose Vial contains a volume of 0.45 mL, supplied as a frozen suspension that does not contain preservative. Each vial must be thawed and diluted prior to administration.
- Vials may be thawed in the refrigerator [2°C to 8°C (35°F to 46°F)] or at room temperature [up to 25°C (77°F)] [*see How Supplied/Storage and Handling (19)*].
- Refer to thawing instructions in the panels below.

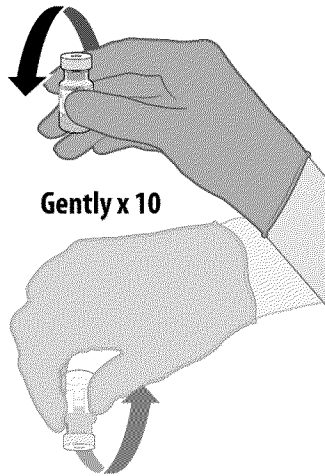
Dilution

- Dilute the vial contents using 1.8 mL of 0.9% Sodium Chloride Injection, USP (not provided) to form the Pfizer-BioNTech COVID-19 Vaccine. Do not add more than 1.8 mL of diluent.
- ONLY use 0.9% Sodium Chloride Injection, USP as the diluent. This diluent is not packaged with the vaccine and must be sourced separately. Do not use bacteriostatic 0.9% Sodium Chloride Injection or any other diluent.
- After dilution, one vial contains 6 doses of 0.3 mL. Vial labels and cartons may state that after dilution, a vial contains 5 doses of 0.3 mL. The information in this Full EUA Prescribing Information regarding the number of doses per vial after dilution supersedes the number of doses stated on vial labels and cartons.
- Refer to dilution and dose preparation instructions in the panels below.

THAWING PRIOR TO DILUTION

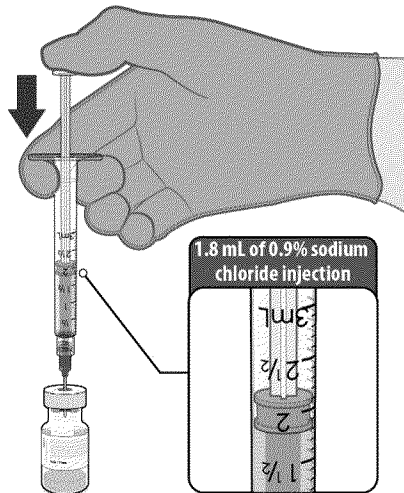


- Thaw vial(s) of Pfizer-BioNTech COVID-19 Vaccine before use either by:
 - Allowing vial(s) to thaw in the refrigerator [2°C to 8°C (35°F to 46°F)]. A carton of vials may take up to 3 hours to thaw, and thawed vials can be stored in the refrigerator for up to 1 month.
 - Allowing vial(s) to sit at room temperature [up to 25°C (77°F)] for 30 minutes.
- Using either thawing method, vials must reach room temperature before dilution and must be diluted within 2 hours.

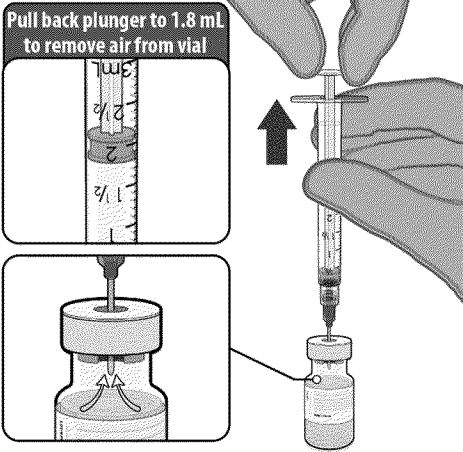
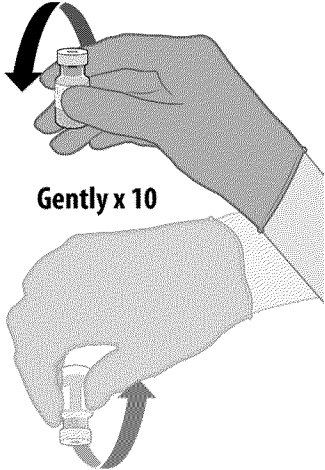
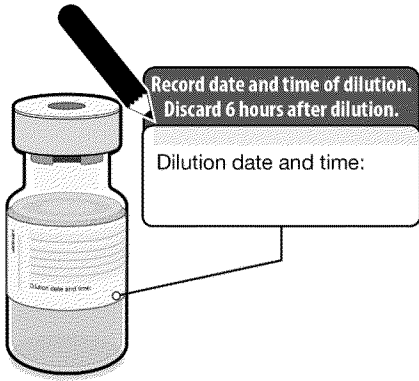


- Before dilution invert vaccine vial gently 10 times.
- Do not shake.
- Inspect the liquid in the vial prior to dilution. The liquid is a white to off-white suspension and may contain white to off-white opaque amorphous particles.
- Do not use if liquid is discolored or if other particles are observed.

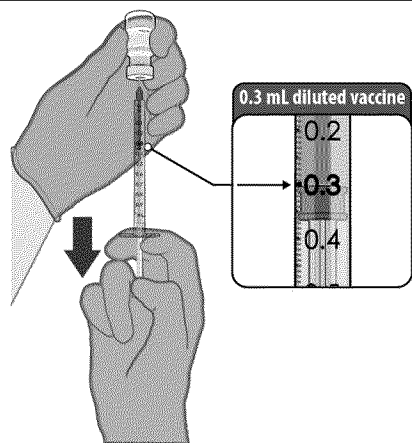
DILUTION



- Obtain sterile 0.9% Sodium Chloride Injection, USP. Use only this as the diluent.
- Using aseptic technique, withdraw 1.8 mL of diluent into a transfer syringe (21-gauge or narrower needle).
- Cleanse the vaccine vial stopper with a single-use antiseptic swab.
- Add 1.8 mL of 0.9% Sodium Chloride Injection, USP into the vaccine vial.

	<ul style="list-style-type: none"> Equalize vial pressure before removing the needle from the vial by withdrawing 1.8 mL air into the empty diluent syringe.
	<ul style="list-style-type: none"> Gently invert the vial containing the Pfizer-BioNTech COVID-19 Vaccine 10 times to mix. <u>Do not shake.</u> Inspect the vaccine in the vial. The vaccine will be an off-white suspension. Do not use if vaccine is discolored or contains particulate matter.
	<ul style="list-style-type: none"> Record the date and time of dilution on the Pfizer-BioNTech COVID-19 Vaccine vial label. Store between 2°C to 25°C (35°F to 77°F). Discard any unused vaccine 6 hours after dilution.

PREPARATION OF INDIVIDUAL 0.3 mL DOSES OF PFIZER-BIONTECH COVID-19 VACCINE



- Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab, and withdraw 0.3 mL of the Pfizer-BioNTech COVID-19 Vaccine preferentially using low dead-volume syringes and/or needles.
- Each dose must contain 0.3 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume.
- Administer immediately.

2.2 Administration Information

Visually inspect each dose in the dosing syringe prior to administration. The vaccine will be an off-white suspension. During the visual inspection,

- verify the final dosing volume of 0.3 mL.
- confirm there are no particulates and that no discoloration is observed.
- do not administer if vaccine is discolored or contains particulate matter.

Administer the Pfizer-BioNTech COVID-19 Vaccine intramuscularly.

After dilution, vials of Pfizer-BioNTech COVID-19 Vaccine contain six doses of 0.3 mL of vaccine. Low dead-volume syringes and/or needles can be used to extract six doses from a single vial. If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial. Irrespective of the type of syringe and needle:

- Each dose must contain 0.3 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume.
- Do not pool excess vaccine from multiple vials.

2.3 Vaccination Schedule for Individuals 12 Years of Age and Older

The Pfizer-BioNTech COVID-19 Vaccine is administered intramuscularly as a series of two doses (0.3 mL each) three weeks apart.

There are no data available on the interchangeability of the Pfizer-BioNTech COVID-19 Vaccine with other COVID-19 vaccines to complete the vaccination series. Individuals who have received one dose of Pfizer-BioNTech COVID-19 Vaccine should receive a second dose of Pfizer-BioNTech COVID-19 Vaccine to complete the vaccination series.

3 DOSAGE FORMS AND STRENGTHS

Pfizer-BioNTech COVID-19 Vaccine is a suspension for injection. After preparation, a single dose is 0.3 mL.

4 CONTRAINDICATIONS

Do not administer Pfizer-BioNTech COVID-19 Vaccine to individuals with known history of a severe allergic reaction (e.g., anaphylaxis) to any component of the Pfizer-BioNTech COVID-19 Vaccine [see Description (13)].

5 WARNINGS AND PRECAUTIONS

5.1 Management of Acute Allergic Reactions

Appropriate medical treatment used to manage immediate allergic reactions must be immediately available in the event an acute anaphylactic reaction occurs following administration of Pfizer-BioNTech COVID-19 Vaccine.

Monitor Pfizer-BioNTech COVID-19 Vaccine recipients for the occurrence of immediate adverse reactions according to the Centers for Disease Control and Prevention guidelines (<https://www.cdc.gov/vaccines/covid-19/clinical-considerations/managing-anaphylaxis.html>).

5.2 Myocarditis and Pericarditis

Reports of adverse events following use of the Pfizer-BioNTech COVID-19 Vaccine under EUA suggest increased risks of myocarditis and pericarditis, particularly following the second dose. Typically, onset of symptoms has been within a few days following receipt of the Pfizer-BioNTech COVID-19 Vaccine. Available data from short-term follow-up suggest that most individuals have had resolution of symptoms, but information is not yet available about potential long-term sequelae. The decision to administer the Pfizer-BioNTech COVID-19 Vaccine to an individual with a history of myocarditis or pericarditis should take into account the individual's clinical circumstances. The CDC has published clinical considerations relevant to myocarditis and pericarditis associated with administration of the Pfizer-BioNTech COVID-19 Vaccine - (<https://www.cdc.gov/vaccines/covid-19/clinical-considerations/myocarditis.html>).

5.25.3 Syncope

Syncope (fainting) may occur in association with administration of injectable vaccines, in particular in adolescents. Procedures should be in place to avoid injury from fainting.

5.35.4 Altered Immunocompetence

Immunocompromised persons, including individuals receiving immunosuppressant therapy, may have a diminished immune response to the Pfizer-BioNTech COVID-19 Vaccine.

5.45.5 Limitation of Effectiveness

The Pfizer-BioNTech COVID-19 Vaccine may not protect all vaccine recipients.

6 OVERALL SAFETY SUMMARY

It is **MANDATORY** for vaccination providers to report to the Vaccine Adverse Event Reporting System (VAERS) all vaccine administration errors, all serious adverse events, cases of Multisystem Inflammatory Syndrome (MIS) in adults and children, and hospitalized or fatal cases of COVID-19 following vaccination with the Pfizer-BioNTech COVID-19 Vaccine. To the extent feasible, provide a copy of the VAERS form to Pfizer Inc. Please see the REQUIREMENTS AND INSTRUCTIONS FOR

REPORTING ADVERSE EVENTS AND VACCINE ADMINISTRATION ERRORS section for details on reporting to VAERS and Pfizer Inc.

In clinical studies, adverse reactions in participants 16 years of age and older included pain at the injection site (84.1%), fatigue (62.9%), headache (55.1%), muscle pain (38.3%), chills (31.9%), joint pain (23.6%), fever (14.2%), injection site swelling (10.5%), injection site redness (9.5%), nausea (1.1%), malaise (0.5%), and lymphadenopathy (0.3%).

In a clinical study, adverse reactions in adolescents 12 through 15 years of age included pain at the injection site (90.5%), fatigue (77.5%), headache (75.5%), chills (49.2%), muscle pain (42.2%), fever (24.3%), joint pain (20.2%), injection site swelling (9.2%), injection site redness (8.6%), lymphadenopathy (0.8%), and nausea (0.4%).

Severe allergic reactions, including anaphylaxis, have been reported following administration of the Pfizer-BioNTech COVID-19 Vaccine outside of clinical trials.

Myocarditis and pericarditis have been reported following administration of the Pfizer-BioNTech COVID-19 Vaccine outside of clinical trials.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of Pfizer-BioNTech COVID-19 Vaccine was evaluated in participants 12 years of age and older in two clinical studies conducted in the United States, Europe, Turkey, South Africa, and South America. Study BNT162-01 (Study 1) was a Phase 1/2, two-part, dose-escalation trial that enrolled 60 participants, 18 through 55 years of age. Study C4591001 (Study 2) is a Phase 1/2/3, multicenter, multinational, randomized, saline placebo-controlled, observer-blind, dose-finding, vaccine candidate-selection (Phase 1) and efficacy (Phase 2/3) study that has enrolled approximately 46,000 participants, 12 years of age or older. Of these, approximately 43,448 participants (21,720 Pfizer-BioNTech COVID-19 Vaccine; 21,728 placebo) in Phase 2/3 are 16 years of age or older (including 138 and 145 adolescents 16 and 17 years of age in the vaccine and placebo groups, respectively) and 2,260 adolescents are 12 through 15 years of age (1,131 and 1,129 in the vaccine and placebo groups, respectively).

In Study 2, all participants 12 to <16 years of age, and participants 16 years of age and older in the reactogenicity subset, were monitored for solicited local and systemic reactions and use of antipyretic medication after each vaccination in an electronic diary. Participants are being monitored for unsolicited adverse events, including serious adverse events, throughout the study [from Dose 1 through 1 month (all unsolicited adverse events) or 6 months (serious adverse events) after the last vaccination]. Tables 1 through 6 present the frequency and severity of solicited local and systemic reactions, respectively, within 7 days following each dose of Pfizer-BioNTech COVID 19 Vaccine and placebo.

Participants 16 Years of Age and Older

At the time of the analysis of Study 2 for the EUA, 37,586 (18,801 Pfizer-BioNTech COVID-19 Vaccine and 18,785 placebo) participants 16 years of age or older had been followed for a median of 2 months after the second dose of Pfizer-BioNTech COVID-19 Vaccine.

The safety evaluation in Study 2 is ongoing. The safety population includes participants 16 years and older enrolled by October 9, 2020, and includes safety data accrued through November 14, 2020.

Demographic characteristics in Study 2 were generally similar with regard to age, gender, race, and ethnicity among participants who received Pfizer-BioNTech COVID-19 Vaccine and those who received placebo. Overall, among the total participants who received either the Pfizer-BioNTech COVID-19 Vaccine or placebo, 50.6% were male and 49.4% were female, 83.1% were White, 9.1% were Black or African American, 28.0% were Hispanic/Latino, 4.3% were Asian, and 0.5% were American Indian/Alaska Native.

Solicited Local and Systemic Adverse Reactions

Across both age groups, 18 through 55 years of age and 56 years and older, the mean duration of pain at the injection site after Dose 2 was 2.5 days (range 1 to 36 days), for redness 2.6 days (range 1 to 34 days), and for

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swelling 2.3 days (range 1 to 34 days) for participants in the Pfizer-BioNTech COVID-19 Vaccine group.

Solicited reactogenicity data in 16 and 17 year-old participants are limited.

Table 1: Study 2 – Frequency and Percentages of Participants with Solicited Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Participants 18 Through 55 Years of Age[‡] – Reactogenicity Subset of the Safety Population*

	Pfizer-BioNTech COVID-19 Vaccine Dose 1 N^a=2291 n^b (%)	Placebo Dose 1 N^a=2298 n^b (%)	Pfizer-BioNTech COVID-19 Vaccine Dose 2 N^a=2098 n^b (%)	Placebo Dose 2 N^a=2103 n^b (%)
Redness^c				
Any (>2 cm)	104 (4.5)	26 (1.1)	123 (5.9)	14 (0.7)
Mild	70 (3.1)	16 (0.7)	73 (3.5)	8 (0.4)
Moderate	28 (1.2)	6 (0.3)	40 (1.9)	6 (0.3)
Severe	6 (0.3)	4 (0.2)	10 (0.5)	0 (0.0)
Swelling^c				
Any (>2 cm)	132 (5.8)	11 (0.5)	132 (6.3)	5 (0.2)
Mild	88 (3.8)	3 (0.1)	80 (3.8)	3 (0.1)
Moderate	39 (1.7)	5 (0.2)	45 (2.1)	2 (0.1)
Severe	5 (0.2)	3 (0.1)	7 (0.3)	0 (0.0)
Pain at the injection site^d				
Any	1904 (83.1)	322 (14.0)	1632 (77.8)	245 (11.7)
Mild	1170 (51.1)	308 (13.4)	1039 (49.5)	225 (10.7)
Moderate	710 (31.0)	12 (0.5)	568 (27.1)	20 (1.0)
Severe	24 (1.0)	2 (0.1)	25 (1.2)	0 (0.0)

Note: Reactions were collected in the electronic diary (e-diary) from Day 1 to Day 7 after vaccination.

a. N = Number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose.

b. n = Number of participants with the specified reaction.

c. Mild: >2.0 to ≤5.0 cm; Moderate: >5.0 to ≤10.0 cm; Severe: >10.0 cm.

d. Mild: does not interfere with activity; Moderate: interferes with activity; Severe: prevents daily activity.

[‡] Eight participants were between 16 and 17 years of age.

* Randomized participants in the safety analysis population who received at least 1 dose of the study intervention.

Table 2: Study 2 – Frequency and Percentages of Participants with Solicited Systemic Reactions, by Maximum Severity, Within 7 Days After Each Dose – Participants 18 Through 55 Years of Age[‡] – Reactogenicity Subset of the Safety Population*

	Pfizer-BioNTech COVID-19 Vaccine Dose 1 N^a=2291 n^b (%)	Placebo Dose 1 N^a=2298 n^b (%)	Pfizer-BioNTech COVID-19 Vaccine Dose 2 N^a=2098 n^b (%)	Placebo Dose 2 N^a=2103 n^b (%)
Fever				
≥38.0°C	85 (3.7)	20 (0.9)	331 (15.8)	10 (0.5)
≥38.0°C to 38.4°C	64 (2.8)	10 (0.4)	194 (9.2)	5 (0.2)
>38.4°C to 38.9°C	15 (0.7)	5 (0.2)	110 (5.2)	3 (0.1)
>38.9°C to 40.0°C	6 (0.3)	3 (0.1)	26 (1.2)	2 (0.1)
>40.0°C	0 (0.0)	2 (0.1)	1 (0.0)	0 (0.0)
Fatigue^c				
Any	1085 (47.4)	767 (33.4)	1247 (59.4)	479 (22.8)
Mild	597 (26.1)	467 (20.3)	442 (21.1)	248 (11.8)
Moderate	455 (19.9)	289 (12.6)	708 (33.7)	217 (10.3)
Severe	33 (1.4)	11 (0.5)	97 (4.6)	14 (0.7)

	Pfizer-BioNTech COVID-19 Vaccine Dose 1 N^a=2291 n^b (%)	Placebo Dose 1 N^a=2298 n^b (%)	Pfizer-BioNTech COVID-19 Vaccine Dose 2 N^a=2098 n^b (%)	Placebo Dose 2 N^a=2103 n^b (%)
Headache^c				
Any	959 (41.9)	775 (33.7)	1085 (51.7)	506 (24.1)
Mild	628 (27.4)	505 (22.0)	538 (25.6)	321 (15.3)
Moderate	308 (13.4)	251 (10.9)	480 (22.9)	170 (8.1)
Severe	23 (1.0)	19 (0.8)	67 (3.2)	15 (0.7)
Chills^c				
Any	321 (14.0)	146 (6.4)	737 (35.1)	79 (3.8)
Mild	230 (10.0)	111 (4.8)	359 (17.1)	65 (3.1)
Moderate	82 (3.6)	33 (1.4)	333 (15.9)	14 (0.7)
Severe	9 (0.4)	2 (0.1)	45 (2.1)	0 (0.0)
Vomiting^d				
Any	28 (1.2)	28 (1.2)	40 (1.9)	25 (1.2)
Mild	24 (1.0)	22 (1.0)	28 (1.3)	16 (0.8)
Moderate	4 (0.2)	5 (0.2)	8 (0.4)	9 (0.4)
Severe	0 (0.0)	1 (0.0)	4 (0.2)	0 (0.0)
Diarrhea^e				
Any	255 (11.1)	270 (11.7)	219 (10.4)	177 (8.4)
Mild	206 (9.0)	217 (9.4)	179 (8.5)	144 (6.8)
Moderate	46 (2.0)	52 (2.3)	36 (1.7)	32 (1.5)
Severe	3 (0.1)	1 (0.0)	4 (0.2)	1 (0.0)
New or worsened muscle pain^c				
Any	487 (21.3)	249 (10.8)	783 (37.3)	173 (8.2)
Mild	256 (11.2)	175 (7.6)	326 (15.5)	111 (5.3)
Moderate	218 (9.5)	72 (3.1)	410 (19.5)	59 (2.8)
Severe	13 (0.6)	2 (0.1)	47 (2.2)	3 (0.1)
New or worsened joint pain^c				
Any	251 (11.0)	138 (6.0)	459 (21.9)	109 (5.2)
Mild	147 (6.4)	95 (4.1)	205 (9.8)	54 (2.6)
Moderate	99 (4.3)	43 (1.9)	234 (11.2)	51 (2.4)
Severe	5 (0.2)	0 (0.0)	20 (1.0)	4 (0.2)
Use of antipyretic or pain medication^f	638 (27.8)	332 (14.4)	945 (45.0)	266 (12.6)

Note: Events and use of antipyretic or pain medication were collected in the electronic diary (e-diary) from Day 1 to Day 7 after each dose.

a. N = Number of participants reporting at least 1 yes or no response for the specified event after the specified dose.

b. n = Number of participants with the specified reaction.

c. Mild: does not interfere with activity; Moderate: some interference with activity; Severe: prevents daily activity.

d. Mild: 1 to 2 times in 24 hours; Moderate: >2 times in 24 hours; Severe: requires intravenous hydration.

e. Mild: 2 to 3 loose stools in 24 hours; Moderate: 4 to 5 loose stools in 24 hours; Severe: 6 or more loose stools in 24 hours.

f. Severity was not collected for use of antipyretic or pain medication.

‡ Eight participants were between 16 and 17 years of age.

* Randomized participants in the safety analysis population who received at least 1 dose of the study intervention.

Table 3: Study 2 – Frequency and Percentages of Participants with Solicited Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Participants 56 Years of Age and Older – Reactogenicity Subset of the Safety Population*

	Pfizer-BioNTech COVID-19 Vaccine Dose 1 N^a=1802 n^b (%)	Placebo Dose 1 N^a=1792 n^b (%)	Pfizer-BioNTech COVID-19 Vaccine Dose 2 N^a=1660 n^b (%)	Placebo Dose 2 N^a=1646 n^b (%)
Redness^c				
Any (>2 cm)	85 (4.7)	19 (1.1)	120 (7.2)	12 (0.7)
Mild	55 (3.1)	12 (0.7)	59 (3.6)	8 (0.5)
Moderate	27 (1.5)	5 (0.3)	53 (3.2)	3 (0.2)
Severe	3 (0.2)	2 (0.1)	8 (0.5)	1 (0.1)
Swelling^c				
Any (>2 cm)	118 (6.5)	21 (1.2)	124 (7.5)	11 (0.7)
Mild	71 (3.9)	10 (0.6)	68 (4.1)	5 (0.3)
Moderate	45 (2.5)	11 (0.6)	53 (3.2)	5 (0.3)
Severe	2 (0.1)	0 (0.0)	3 (0.2)	1 (0.1)
Pain at the injection site^d				
Any (>2 cm)	1282 (71.1)	166 (9.3)	1098 (66.1)	127 (7.7)
Mild	1008 (55.9)	160 (8.9)	792 (47.7)	125 (7.6)
Moderate	270 (15.0)	6 (0.3)	298 (18.0)	2 (0.1)
Severe	4 (0.2)	0 (0.0)	8 (0.5)	0 (0.0)

Note: Reactions were collected in the electronic diary (e-diary) from Day 1 to Day 7 after vaccination.

a. N = Number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose.

b. n = Number of participants with the specified reaction.

c. Mild: >2.0 to ≤5.0 cm; Moderate: >5.0 to ≤10.0 cm; Severe: >10.0 cm.

d. Mild: does not interfere with activity; Moderate: interferes with activity; Severe: prevents daily activity.

* Randomized participants in the safety analysis population who received at least 1 dose of the study intervention.

Table 4: Study 2 – Frequency and Percentages of Participants with Solicited Systemic Reactions, by Maximum Severity, Within 7 Days After Each Dose – Participants 56 Years of Age and Older – Reactogenicity Subset of the Safety Population*

	Pfizer-BioNTech COVID-19 Vaccine Dose 1 N^a=1802 n^b (%)	Placebo Dose 1 N^a=1792 n^b (%)	Pfizer-BioNTech COVID-19 Vaccine Dose 2 N^a=1660 n^b (%)	Placebo Dose 2 N^a=1646 n^b (%)
Fever				
≥38.0°C	26 (1.4)	7 (0.4)	181 (10.9)	4 (0.2)
≥38.0°C to 38.4°C	23 (1.3)	2 (0.1)	131 (7.9)	2 (0.1)
>38.4°C to 38.9°C	1 (0.1)	3 (0.2)	45 (2.7)	1 (0.1)
>38.9°C to 40.0°C	1 (0.1)	2 (0.1)	5 (0.3)	1 (0.1)
>40.0°C	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Fatigue^c				
Any	615 (34.1)	405 (22.6)	839 (50.5)	277 (16.8)
Mild	373 (20.7)	252 (14.1)	351 (21.1)	161 (9.8)
Moderate	240 (13.3)	150 (8.4)	442 (26.6)	114 (6.9)
Severe	2 (0.1)	3 (0.2)	46 (2.8)	2 (0.1)

	Pfizer-BioNTech COVID-19 Vaccine Dose 1 N^a=1802 n^b (%)	Placebo Dose 1 N^a=1792 n^b (%)	Pfizer-BioNTech COVID-19 Vaccine Dose 2 N^a=1660 n^b (%)	Placebo Dose 2 N^a=1646 n^b (%)
Headache^c				
Any	454 (25.2)	325 (18.1)	647 (39.0)	229 (13.9)
Mild	348 (19.3)	242 (13.5)	422 (25.4)	165 (10.0)
Moderate	104 (5.8)	80 (4.5)	216 (13.0)	60 (3.6)
Severe	2 (0.1)	3 (0.2)	9 (0.5)	4 (0.2)
Chills^c				
Any	113 (6.3)	57 (3.2)	377 (22.7)	46 (2.8)
Mild	87 (4.8)	40 (2.2)	199 (12.0)	35 (2.1)
Moderate	26 (1.4)	16 (0.9)	161 (9.7)	11 (0.7)
Severe	0 (0.0)	1 (0.1)	17 (1.0)	0 (0.0)
Vomiting^d				
Any	9 (0.5)	9 (0.5)	11 (0.7)	5 (0.3)
Mild	8 (0.4)	9 (0.5)	9 (0.5)	5 (0.3)
Moderate	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)
Severe	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Diarrhea^e				
Any	147 (8.2)	118 (6.6)	137 (8.3)	99 (6.0)
Mild	118 (6.5)	100 (5.6)	114 (6.9)	73 (4.4)
Moderate	26 (1.4)	17 (0.9)	21 (1.3)	22 (1.3)
Severe	3 (0.2)	1 (0.1)	2 (0.1)	4 (0.2)
New or worsened muscle pain^c				
Any	251 (13.9)	149 (8.3)	477 (28.7)	87 (5.3)
Mild	168 (9.3)	100 (5.6)	202 (12.2)	57 (3.5)
Moderate	82 (4.6)	46 (2.6)	259 (15.6)	29 (1.8)
Severe	1 (0.1)	3 (0.2)	16 (1.0)	1 (0.1)
New or worsened joint pain^c				
Any	155 (8.6)	109 (6.1)	313 (18.9)	61 (3.7)
Mild	101 (5.6)	68 (3.8)	161 (9.7)	35 (2.1)
Moderate	52 (2.9)	40 (2.2)	145 (8.7)	25 (1.5)
Severe	2 (0.1)	1 (0.1)	7 (0.4)	1 (0.1)
Use of antipyretic or pain medication	358 (19.9)	213 (11.9)	625 (37.7)	161 (9.8)

Note: Events and use of antipyretic or pain medication were collected in the electronic diary (e-diary) from Day 1 to Day 7 after each dose.

a. N = Number of participants reporting at least 1 yes or no response for the specified event after the specified dose.

b. n = Number of participants with the specified reaction.

c. Mild: does not interfere with activity; Moderate: some interference with activity; Severe: prevents daily activity.

d. Mild: 1 to 2 times in 24 hours; Moderate: >2 times in 24 hours; Severe: requires intravenous hydration.

e. Mild: 2 to 3 loose stools in 24 hours; Moderate: 4 to 5 loose stools in 24 hours; Severe: 6 or more loose stools in 24 hours.

* Randomized participants in the safety analysis population who received at least 1 dose of the study intervention.

Serious Adverse Events

In Study 2, among participants 16 through 55 years of age who had received at least 1 dose of vaccine or placebo (Pfizer-BioNTech COVID-19 Vaccine = 10,841; placebo = 10,851), serious adverse events from Dose 1 through up to 30 days after Dose 2 in ongoing follow-up were reported by 0.4% of Pfizer-BioNTech COVID-19 Vaccine recipients and by 0.3% of placebo recipients. In a similar analysis, in participants 56 years of age and older (Pfizer-BioNTech COVID-19 Vaccine = 7,960, placebo = 7,934), serious adverse events were reported by 0.8% of Pfizer-BioNTech COVID-19 Vaccine recipients and by 0.6% of placebo recipients who received at least 1 dose of Pfizer-BioNTech COVID-19 Vaccine or placebo, respectively. In these analyses, 91.6% of study participants had at least 30 days of follow-up after Dose 2.

Appendicitis was reported as a serious adverse event for 12 participants, and numerically higher in the vaccine group, 8 vaccine participants and 4 placebo participants. Currently available information is insufficient to determine a causal relationship with the vaccine. There were no other notable patterns or numerical imbalances between treatment groups for specific categories of serious adverse events (including neurologic, neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to Pfizer-BioNTech COVID-19 Vaccine.

Non-Serious Adverse Events

In Study 2 in which 10,841 participants 16 through 55 years of age received Pfizer-BioNTech COVID-19 Vaccine and 10,851 participants received placebo, non-serious adverse events from Dose 1 through up to 30 days after Dose 2 in ongoing follow-up were reported in 29.3% of participants who received Pfizer-BioNTech COVID-19 Vaccine and 13.2% of participants in the placebo group, for participants who received at least 1 dose. Overall in a similar analysis in which 7960 participants 56 years of age and older received Pfizer-BioNTech COVID-19 Vaccine, non-serious adverse events within 30 days were reported in 23.8% of participants who received Pfizer-BioNTech COVID-19 Vaccine and 11.7% of participants in the placebo group, for participants who received at least 1 dose. In these analyses, 91.6% of study participants had at least 30 days of follow-up after Dose 2.

The higher frequency of reported unsolicited non-serious adverse events among Pfizer-BioNTech COVID-19 Vaccine recipients compared to placebo recipients was primarily attributed to local and systemic adverse events reported during the first 7 days following vaccination that are consistent with adverse reactions solicited among participants in the reactogenicity subset and presented in Tables 3 and 4. From Dose 1 through 30 days after Dose 2, reports of lymphadenopathy were imbalanced with notably more cases in the Pfizer-BioNTech COVID-19 Vaccine group (64) vs. the placebo group (6), which is plausibly related to vaccination. Throughout the safety follow-up period to date, Bell's palsy (facial paralysis) was reported by four participants in the Pfizer-BioNTech COVID-19 Vaccine group. Onset of facial paralysis was Day 37 after Dose 1 (participant did not receive Dose 2) and Days 3, 9, and 48 after Dose 2. No cases of Bell's palsy were reported in the placebo group. Currently available information is insufficient to determine a causal relationship with the vaccine. There were no other notable patterns or numerical imbalances between treatment groups for specific categories of non-serious adverse events (including other neurologic or neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to Pfizer-BioNTech COVID-19 Vaccine.

Adolescents 12 Through 15 Years of Age

In an analysis of Study 2, based on data up to the cutoff date of March 13, 2021, 2,260 adolescents (1,131 Pfizer-BioNTech COVID-19 Vaccine; 1,129 placebo) were 12 through 15 years of age. Of these, 1,308 (660 Pfizer-BioNTech COVID-19 Vaccine and 648 placebo) adolescents have been followed for at least

2 months after the second dose of Pfizer-BioNTech COVID-19 Vaccine. The safety evaluation in Study 2 is ongoing.

Demographic characteristics in Study 2 were generally similar with regard to age, gender, race, and ethnicity among adolescents who received Pfizer-BioNTech COVID-19 Vaccine and those who received placebo. Overall, among the adolescents who received the Pfizer-BioNTech COVID-19 Vaccine, 50.1% were male and 49.9% were female, 85.9% were White, 4.6% were Black or African American, 11.7% were Hispanic/Latino, 6.4% were Asian, and 0.4% were American Indian/Alaska Native.

Solicited Local and Systemic Adverse Reactions

The mean duration of pain at the injection site after Dose 1 was 2.4 days (range 1 to 10 days), for redness 2.4 days (range 1 to 16 days), and for swelling 1.9 days (range 1 to 5 days) for adolescents in the Pfizer-BioNTech COVID-19 Vaccine group.

Table 5: Study 2 – Frequency and Percentages of Adolescents With Solicited Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Adolescents 12 Through 15 Years of Age – Safety Population*

	Pfizer-BioNTech COVID-19 Vaccine Dose 1 N^a=1127 n^b (%)	Placebo Dose 1 N^a=1127 n^b (%)	Pfizer-BioNTech COVID-19 Vaccine Dose 2 N^a=1097 n^b (%)	Placebo Dose 2 N^a=1078 n^b (%)
Redness^c				
Any (>2 cm)	65 (5.8)	12 (1.1)	55 (5.0)	10 (0.9)
Mild	44 (3.9)	11 (1.0)	29 (2.6)	8 (0.7)
Moderate	20 (1.8)	1 (0.1)	26 (2.4)	2 (0.2)
Severe	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Swelling^c				
Any (>2 cm)	78 (6.9)	11 (1.0)	54 (4.9)	6 (0.6)
Mild	55 (4.9)	9 (0.8)	36 (3.3)	4 (0.4)
Moderate	23 (2.0)	2 (0.2)	18 (1.6)	2 (0.2)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pain at the injection site^d				
Any	971 (86.2)	263 (23.3)	866 (78.9)	193 (17.9)
Mild	467 (41.4)	227 (20.1)	466 (42.5)	164 (15.2)
Moderate	493 (43.7)	36 (3.2)	393 (35.8)	29 (2.7)
Severe	11 (1.0)	0 (0.0)	7 (0.6)	0 (0.0)

Note: Reactions were collected in the electronic diary (e-diary) from Day 1 to Day 7 after vaccination.

a. N = Number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose.

b. n = Number of participants with the specified reaction.

c. Mild: >2.0 to ≤5.0 cm; Moderate: >5.0 to ≤10.0 cm; Severe: >10.0 cm.

d. Mild: does not interfere with activity; Moderate: interferes with activity; Severe: prevents daily activity.

* Randomized participants in the safety analysis population who received at least 1 dose of the study intervention.

Table 6: Study 2 – Frequency and Percentages of Adolescents with Solicited Systemic Reactions, by Maximum Severity, Within 7 Days After Each Dose – Adolescents 12 Through 15 Years of Age – Safety Population*

	Pfizer-BioNTech COVID-19 Vaccine Dose 1 N^a=1127 n^b (%)	Placebo Dose 1 N^a=1127 n^b (%)	Pfizer-BioNTech COVID-19 Vaccine Dose 2 N^a=1097 n^b (%)	Placebo Dose 2 N^a=1078 n^b (%)
Fever				
≥38.0°C	114 (10.1)	12 (1.1)	215 (19.6)	7 (0.6)
≥38.0°C to 38.4°C	74 (6.6)	8 (0.7)	107 (9.8)	5 (0.5)
>38.4°C to 38.9°C	29 (2.6)	2 (0.2)	83 (7.6)	1 (0.1)
>38.9°C to 40.0°C	10 (0.9)	2 (0.2)	25 (2.3)	1 (0.1)
>40.0°C	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Fatigue^c				
Any	677 (60.1)	457 (40.6)	726 (66.2)	264 (24.5)
Mild	278 (24.7)	250 (22.2)	232 (21.1)	133 (12.3)
Moderate	384 (34.1)	199 (17.7)	468 (42.7)	127 (11.8)
Severe	15 (1.3)	8 (0.7)	26 (2.4)	4 (0.4)
Headache^c				
Any	623 (55.3)	396 (35.1)	708 (64.5)	263 (24.4)
Mild	361 (32.0)	256 (22.7)	302 (27.5)	169 (15.7)
Moderate	251 (22.3)	131 (11.6)	384 (35.0)	93 (8.6)
Severe	11 (1.0)	9 (0.8)	22 (2.0)	1 (0.1)
Chills^c				
Any	311 (27.6)	109 (9.7)	455 (41.5)	73 (6.8)
Mild	195 (17.3)	82 (7.3)	221 (20.1)	52 (4.8)
Moderate	111 (9.8)	25 (2.2)	214 (19.5)	21 (1.9)
Severe	5 (0.4)	2 (0.2)	20 (1.8)	0 (0.0)
Vomiting^d				
Any	31 (2.8)	10 (0.9)	29 (2.6)	12 (1.1)
Mild	30 (2.7)	8 (0.7)	25 (2.3)	11 (1.0)
Moderate	0 (0.0)	2 (0.2)	4 (0.4)	1 (0.1)
Severe	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Diarrhea^c				
Any	90 (8.0)	82 (7.3)	65 (5.9)	43 (4.0)
Mild	77 (6.8)	72 (6.4)	59 (5.4)	38 (3.5)
Moderate	13 (1.2)	10 (0.9)	6 (0.5)	5 (0.5)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
New or worsened muscle pain^c				
Any	272 (24.1)	148 (13.1)	355 (32.4)	90 (8.3)
Mild	125 (11.1)	88 (7.8)	152 (13.9)	51 (4.7)
Moderate	145 (12.9)	60 (5.3)	197 (18.0)	37 (3.4)
Severe	2 (0.2)	0 (0.0)	6 (0.5)	2 (0.2)

	Pfizer-BioNTech COVID-19 Vaccine Dose 1 N^a=1127 n^b (%)	Placebo Dose 1 N^a=1127 n^b (%)	Pfizer-BioNTech COVID-19 Vaccine Dose 2 N^a=1097 n^b (%)	Placebo Dose 2 N^a=1078 n^b (%)
New or worsened joint pain ^c				
Any	109 (9.7)	77 (6.8)	173 (15.8)	51 (4.7)
Mild	66 (5.9)	50 (4.4)	91 (8.3)	30 (2.8)
Moderate	42 (3.7)	27 (2.4)	78 (7.1)	21 (1.9)
Severe	1 (0.1)	0 (0.0)	4 (0.4)	0 (0.0)
Use of antipyretic or pain medication ^f	413 (36.6)	111 (9.8)	557 (50.8)	95 (8.8)

Note: Events and use of antipyretic or pain medication were collected in the electronic diary (e-diary) from Day 1 to Day 7 after each dose.

a. N = Number of participants reporting at least 1 yes or no response for the specified event after the specified dose.

b. n = Number of participants with the specified reaction.

c. Mild: does not interfere with activity; Moderate: some interference with activity; Severe: prevents daily activity.

d. Mild: 1 to 2 times in 24 hours; Moderate: >2 times in 24 hours; Severe: requires intravenous hydration.

e. Mild: 2 to 3 loose stools in 24 hours; Moderate: 4 to 5 loose stools in 24 hours; Severe: 6 or more loose stools in 24 hours.

f. Severity was not collected for use of antipyretic or pain medication.

* Randomized participants in the safety analysis population who received at least 1 dose of the study intervention.

Unsolicited Adverse Events

In the following analyses of Study 2 in adolescents 12 through 15 years of age (1,131 of whom received Pfizer-BioNTech COVID-19 Vaccine and 1,129 of whom received placebo), 98.3% of study participants had at least 30 days of follow-up after Dose 2.

Serious Adverse Events

Serious adverse events from Dose 1 through up to 30 days after Dose 2 in ongoing follow-up were reported by 0.4% of Pfizer-BioNTech COVID-19 Vaccine recipients and by 0.1% of placebo recipients. There were no notable patterns or numerical imbalances between treatment groups for specific categories of serious adverse events that would suggest a causal relationship to Pfizer-BioNTech COVID-19 Vaccine.

Non-Serious Adverse Events

Non-serious adverse events from Dose 1 through up to 30 days after Dose 2 in ongoing follow-up were reported by 5.8% of Pfizer-BioNTech COVID-19 Vaccine recipients and by 5.8% of placebo recipients. From Dose 1 through 30 days after Dose 2, reports of lymphadenopathy plausibly related to the study intervention were imbalanced, with notably more cases in the Pfizer-BioNTech COVID-19 Vaccine group (7) vs. the placebo group (1). There were no other notable patterns or numerical imbalances between treatment groups for specific categories of non-serious adverse events that would suggest a causal relationship to Pfizer-BioNTech COVID-19 Vaccine.

6.2 Post Authorization Experience

The following adverse reactions have been identified during post authorization use of Pfizer-BioNTech COVID-19 Vaccine. Because these reactions are reported voluntarily, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure.

Cardiac Disorders: myocarditis, pericarditis

Gastrointestinal Disorders: diarrhea, vomiting

Immune System Disorders: severe allergic reactions, including anaphylaxis, and other hypersensitivity reactions (e.g., rash, pruritus, urticaria, angioedema)

~~Gastrointestinal Disorders: diarrhea, vomiting~~

Musculoskeletal and Connective Tissue Disorders: pain in extremity (arm)

8 REQUIREMENTS AND INSTRUCTIONS FOR REPORTING ADVERSE EVENTS AND VACCINE ADMINISTRATION ERRORS

See Overall Safety Summary (Section 6) for additional information.

The vaccination provider enrolled in the federal COVID-19 Vaccination Program is responsible for MANDATORY reporting of the listed events following Pfizer-BioNTech COVID-19 Vaccine to the Vaccine Adverse Event Reporting System (VAERS):

- Vaccine administration errors whether or not associated with an adverse event
- Serious adverse events* (irrespective of attribution to vaccination)
- Cases of Multisystem Inflammatory Syndrome (MIS) in children and adults
- Cases of COVID-19 that result in hospitalization or death

*Serious adverse events are defined as:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- An important medical event that based on appropriate medical judgement may jeopardize the individual and may require medical or surgical intervention to prevent one of the outcomes listed above

Instructions for Reporting to VAERS

The vaccination provider enrolled in the federal COVID-19 Vaccination Program should complete and submit a VAERS form to FDA using one of the following methods:

- Complete and submit the report online: <https://vaers.hhs.gov/reportevent.html>, or
- If you are unable to submit this form electronically, you may fax it to VAERS at 1-877-721-0366. If you need additional help submitting a report you may call the VAERS toll-free information line at 1-800-822-7967 or send an email to info@vaers.org.

IMPORTANT: When reporting adverse events or vaccine administration errors to VAERS, please complete the entire form with detailed information. It is important that the information reported to FDA be as detailed and complete as possible. Information to include:

- Patient demographics (e.g., patient name, date of birth)
- Pertinent medical history
- Pertinent details regarding admission and course of illness
- Concomitant medications
- Timing of adverse event(s) in relationship to administration of the Pfizer-BioNTech COVID-19 Vaccine
- Pertinent laboratory and virology information

- Outcome of the event and any additional follow-up information if it is available at the time of the VAERS report. Subsequent reporting of follow-up information should be completed if additional details become available.

The following steps are highlighted to provide the necessary information for safety tracking:

1. In Box 17, provide information on Pfizer-BioNTech COVID-19 Vaccine and any other vaccines administered on the same day; and in Box 22, provide information on any other vaccines received within one month prior.
2. In Box 18, description of the event:
 - a. Write "Pfizer-BioNTech COVID-19 Vaccine EUA" as the first line.
 - b. Provide a detailed report of vaccine administration error and/or adverse event. It is important to provide detailed information regarding the patient and adverse event/medication error for ongoing safety evaluation of this unapproved vaccine. Please see information to include listed above.
3. Contact information:
 - a. In Box 13, provide the name and contact information of the prescribing healthcare provider or institutional designee who is responsible for the report.
 - b. In Box 14, provide the name and contact information of the best doctor/healthcare professional to contact about the adverse event.
 - c. In Box 15, provide the address of the facility where vaccine was given (NOT the healthcare provider's office address).

Other Reporting Instructions

Vaccination providers may report to VAERS other adverse events that are not required to be reported using the contact information above.

To the extent feasible, report adverse events to Pfizer Inc. using the contact information below or by providing a copy of the VAERS form to Pfizer Inc.

Website	Fax number	Telephone number
www.pfizersafetyreporting.com	1-866-635-8337	1-800-438-1985

10 DRUG INTERACTIONS

There are no data to assess the concomitant administration of the Pfizer-BioNTech COVID-19 Vaccine with other vaccines.

11 USE IN SPECIFIC POPULATIONS

11.1 Pregnancy

Risk Summary

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. Available data on Pfizer-BioNTech COVID-19 Vaccine administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy.

In a reproductive and developmental toxicity study, 0.06 mL of a vaccine formulation containing the same quantity of nucleoside-modified messenger ribonucleic acid (mRNA) (30 mcg) and other ingredients included in a single human dose of Pfizer-BioNTech COVID-19 Vaccine was administered to female rats by the

intramuscular route on four occasions: 21 and 14 days prior to mating, and on gestation days 9 and 20. No vaccine-related adverse effects on female fertility, fetal development, or postnatal development were reported in the study.

11.2 Lactation

Risk Summary

Data are not available to assess the effects of Pfizer-BioNTech COVID-19 Vaccine on the breastfed infant or on milk production/excretion.

11.3 Pediatric Use

Emergency Use Authorization of Pfizer-BioNTech COVID-19 Vaccine in adolescents 12 through 18 years of age is based on safety and effectiveness data in this age group and in adults.

Emergency Use Authorization of Pfizer-BioNTech COVID-19 Vaccine does not include use in individuals younger than 12 years of age.

11.4 Geriatric Use

Clinical studies of Pfizer-BioNTech COVID-19 Vaccine include participants 65 years of age and older and their data contributes to the overall assessment of safety and efficacy [*see Overall Safety Summary (6.1) and Clinical Trial Results and Supporting Data for EUA (18.1)*]. Of the total number of Pfizer-BioNTech COVID-19 Vaccine recipients in Study 2 (N=20,033), 21.4% (n=4,294) were 65 years of age and older and 4.3% (n=860) were 75 years of age and older.

13 DESCRIPTION

The Pfizer-BioNTech COVID-19 Vaccine is supplied as a frozen suspension in multiple dose vials; each vial must be diluted with 1.8 mL of sterile 0.9% Sodium Chloride Injection, USP prior to use to form the vaccine. Each dose of the Pfizer-BioNTech COVID-19 Vaccine contains 30 mcg of a nucleoside-modified messenger RNA (modRNA) encoding the viral spike (S) glycoprotein of SARS-CoV-2.

Each dose of the Pfizer-BioNTech COVID-19 Vaccine also includes the following ingredients: lipids (0.43 mg (4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), 0.05 mg 2[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide, 0.09 mg 1,2-distearoyl-sn-glycero-3-phosphocholine, and 0.2 mg cholesterol), 0.01 mg potassium chloride, 0.01 mg monobasic potassium phosphate, 0.36 mg sodium chloride, 0.07 mg dibasic sodium phosphate dihydrate, and 6 mg sucrose. The diluent (0.9% Sodium Chloride Injection, USP) contributes an additional 2.16 mg sodium chloride per dose.

The Pfizer-BioNTech COVID-19 Vaccine does not contain preservative. The vial stoppers are not made with natural rubber latex.

14 CLINICAL PHARMACOLOGY

14.1 Mechanism of Action

The modRNA in the Pfizer-BioNTech COVID-19 Vaccine is formulated in lipid particles, which enable delivery of the RNA into host cells to allow expression of the SARS-CoV-2 S antigen. The vaccine elicits an immune response to the S antigen, which protects against COVID-19.

18 CLINICAL TRIAL RESULTS AND SUPPORTING DATA FOR EUA

18.1 Efficacy in Participants 16 Years of Age and Older

Study 2 is a multicenter, multinational, Phase 1/2/3, randomized, placebo-controlled, observer-blind, dose-finding, vaccine candidate-selection, and efficacy study in participants 12 years of age and older. Randomization was stratified by age: 12 through 15 years of age, 16 through 55 years of age, or 56 years of age and older, with a minimum of 40% of participants in the ≥ 56 -year stratum. The study excluded participants who were immunocompromised and those who had previous clinical or microbiological diagnosis of COVID-19. Participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, were included as were participants with known stable infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV).

In the Phase 2/3 portion of Study 2, based on data accrued through November 14, 2020, approximately 44,000 participants 12 years of age and older were randomized equally and received 2 doses of Pfizer-BioNTech COVID-19 Vaccine or placebo separated by 21 days. Participants are planned to be followed for up to 24 months, for assessments of safety and efficacy against COVID-19.

The population for the analysis of the primary efficacy endpoint included, 36,621 participants 12 years of age and older (18,242 in the Pfizer-BioNTech COVID-19 Vaccine group and 18,379 in the placebo group) who did not have evidence of prior infection with SARS-CoV-2 through 7 days after the second dose. Table 7 presents the specific demographic characteristics in the studied population.

Table 7: Demographics (population for the primary efficacy endpoint)^a

	Pfizer-BioNTech COVID-19 Vaccine (N=18,242) n (%)	Placebo (N=18,379) n (%)
Sex		
Male	9318 (51.1)	9225 (50.2)
Female	8924 (48.9)	9154 (49.8)
Age (years)		
Mean (SD)	50.6 (15.70)	50.4 (15.81)
Median	52.0	52.0
Min, max	(12, 89)	(12, 91)
Age group		
≥ 12 through 15 years ^b	46 (0.3)	42 (0.2)
≥ 16 through 17 years	66 (0.4)	68 (0.4)
≥ 16 through 64 years	14,216 (77.9)	14,299 (77.8)
≥ 65 through 74 years	3176 (17.4)	3226 (17.6)
≥ 75 years	804 (4.4)	812 (4.4)
Race		
White	15,110 (82.8)	15,301 (83.3)
Black or African American	1617 (8.9)	1617 (8.8)
American Indian or Alaska Native	118 (0.6)	106 (0.6)
Asian	815 (4.5)	810 (4.4)
Native Hawaiian or other Pacific Islander	48 (0.3)	29 (0.2)
Other ^c	534 (2.9)	516 (2.8)

	Pfizer-BioNTech COVID-19 Vaccine (N=18,242) n (%)	Placebo (N=18,379) n (%)
Ethnicity		
Hispanic or Latino	4886 (26.8)	4857 (26.4)
Not Hispanic or Latino	13,253 (72.7)	13,412 (73.0)
Not reported	103 (0.6)	110 (0.6)
Comorbidities ^d		
Yes	8432 (46.2)	8450 (46.0)
No	9810 (53.8)	9929 (54.0)

- a. All eligible randomized participants who receive all vaccination(s) as randomized within the predefined window, have no other important protocol deviations as determined by the clinician, and have no evidence of SARS-CoV-2 infection prior to 7 days after Dose 2.
- b. 100 participants 12 through 15 years of age with limited follow-up in the randomized population received at least one dose (49 in the vaccine group and 51 in the placebo group). Some of these participants were included in the efficacy evaluation depending on the population analyzed. They contributed to exposure information but with no confirmed COVID-19 cases, and did not affect efficacy conclusions.
- c. Includes multiracial and not reported.
- d. Number of participants who have 1 or more comorbidities that increase the risk of severe COVID-19 disease
 - Chronic lung disease (e.g., emphysema and chronic bronchitis, idiopathic pulmonary fibrosis, and cystic fibrosis) or moderate to severe asthma
 - Significant cardiac disease (e.g., heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension)
 - Obesity (body mass index ≥ 30 kg/m²)
 - Diabetes (Type 1, Type 2 or gestational)
 - Liver disease
 - Human Immunodeficiency Virus (HIV) infection (not included in the efficacy evaluation)

The population in the primary efficacy analysis included all participants 12 years of age and older who had been enrolled from July 27, 2020, and followed for the development of COVID-19 through November 14, 2020. Participants 18 through 55 years of age and 56 years of age and older began enrollment from July 27, 2020, 16 through 17 years of age began enrollment from September 16, 2020, and 12 through 15 years of age began enrollment from October 15, 2020.

The vaccine efficacy information is presented in Table 8.

Table 8: Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Age Subgroup – Participants Without Evidence of Infection and Participants With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

First COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection*			
Subgroup	Pfizer-BioNTech COVID-19 Vaccine N ^a =18,198 Cases n1 ^b Surveillance Time ^c (n2 ^d)	Placebo N ^a =18,325 Cases n1 ^b Surveillance Time ^c (n2 ^d)	Vaccine Efficacy % (95% CI)
All subjects ^e	8 2.214 (17,411)	162 2.222 (17,511)	95.0 (90.3, 97.6) ^f
16 through 64 years	7 1.706 (13,549)	143 1.710 (13,618)	95.1 (89.6, 98.1) ^g
65 years and older	1 0.508 (3848)	19 0.511 (3880)	94.7 (66.7, 99.9) ^g
First COVID-19 occurrence from 7 days after Dose 2 in participants with or without evidence of prior SARS-CoV-2 infection			
Subgroup	Pfizer-BioNTech COVID-19 Vaccine N ^a =19,965 Cases n1 ^b Surveillance Time ^c (n2 ^d)	Placebo N ^a =20,172 Cases n1 ^b Surveillance Time ^c (n2 ^d)	Vaccine Efficacy % (95% CI)
All subjects ^e	9 2.332 (18,559)	169 2.345 (18,708)	94.6 (89.9, 97.3) ^f
16 through 64 years	8 1.802 (14,501)	150 1.814 (14,627)	94.6 (89.1, 97.7) ^g
65 years and older	1 0.530 (4044)	19 0.532 (4067)	94.7 (66.8, 99.9) ^g

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhea; vomiting).

* Participants who had no evidence of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

- a. N = Number of participants in the specified group.
- b. n1 = Number of participants meeting the endpoint definition.
- c. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
- d. n2 = Number of participants at risk for the endpoint.
- e. No confirmed cases were identified in adolescents 12 through 15 years of age.
- f. Credible interval for vaccine efficacy (VE) was calculated using a beta-binomial model with a beta (0.700102, 1) prior for $\theta = r(1-VE)/(1+r(1-VE))$, where r is the ratio of surveillance time in the active vaccine group over that in the placebo group.
- g. Confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.

18.2 Efficacy in Adolescents 12 Through 15 Years of Age

A descriptive efficacy analysis of Study 2 has been performed in approximately 2,200 adolescents 12 through 15 years of age evaluating confirmed COVID-19 cases accrued up to a data cutoff date of March 13, 2021.

The efficacy information in adolescents 12 through 15 years of age is presented in Table 9.

Table 9: Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2: Without Evidence of Infection and With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Blinded Placebo-Controlled Follow-up Period, Adolescents 12 Through 15 Years of Age Evaluable Efficacy (7 Days) Population

First COVID-19 occurrence from 7 days after Dose 2 in adolescents 12 through 15 years of age without evidence of prior SARS-CoV-2 infection*			
	Pfizer-BioNTech COVID-19 Vaccine N^a=1005 Cases n1^b Surveillance Time^c (n2^d)	Placebo N^a=978 Cases n1^b Surveillance Time^c (n2^d)	Vaccine Efficacy % (95% CI^e)
Adolescents 12 through 15 years of age	0 0.154 (1001)	16 0.147 (972)	100.0 (75.3, 100.0)
First COVID-19 occurrence from 7 days after Dose 2 in adolescents 12 through 15 years of age with or without evidence of prior SARS-CoV-2 infection			
	Pfizer-BioNTech COVID-19 Vaccine N^a=1119 Cases n1^b Surveillance Time^c (n2^d)	Placebo N^a=1110 Cases n1^b Surveillance Time^c (n2^d)	Vaccine Efficacy % (95% CI^e)
Adolescents 12 through 15 years of age	0 0.170 (1109)	18 0.163 (1094)	100.0 (78.1, 100.0)

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhea; vomiting).

* Participants who had no evidence of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

- N = Number of participants in the specified group.
- n1 = Number of participants meeting the endpoint definition.
- Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
- n2 = Number of participants at risk for the endpoint.
- Confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted for surveillance time.

18.3 Immunogenicity in Adolescents 12 Through 15 Years of Age

In Study 2, an analysis of SARS-CoV-2 50% neutralizing titers 1 month after Dose 2 in a randomly selected subset of participants demonstrated non-inferior immune responses (within 1.5-fold) comparing adolescents 12 through 15 years of age to participants 16 through 25 years of age who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after Dose 2 (Table 10).

Table 10: Summary of Geometric Mean Ratio for 50% Neutralizing Titer – Comparison of Adolescents 12 Through 15 Years of Age to Participants 16 Through 25 Years of Age (Immunogenicity Subset) –Participants Without Evidence of Infection up to 1 Month After Dose 2 – Dose 2 Evaluable Immunogenicity Population

		Pfizer-BioNTech COVID-19 Vaccine			
		12 Through 15 Years n ^a =190	16 Through 25 Years n ^a =170	12 Through 15 Years/ 16 Through 25 Years	
Assay	Time Point ^b	GMT ^c (95% CI ^c)	GMT ^c (95% CI ^c)	GMR ^d (95% CI ^d)	Met Noninferiority Objective ^e (Y/N)
SARS-CoV-2 neutralization assay - NT50 (titer) ^f	1 month after Dose 2	1239.5 (1095.5, 1402.5)	705.1 (621.4, 800.2)	1.76 (1.47, 2.10)	Y

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titer; LLOQ = lower limit of quantitation; NAAT = nucleic-acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Participants who had no serological or virological evidence (up to 1 month after receipt of the last dose) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit up to 1 month after Dose 2 were included in the analysis.

- n = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point.
- Protocol-specified timing for blood sample collection.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times \text{LLOQ}$.
- GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titers (Group 1 [12 through 15 years of age] – Group 2 [16 through 25 years of age]) and the corresponding CI (based on the Student t distribution).
- Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67.
- SARS-CoV-2 50% neutralization titers (NT50) were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralization is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralized.

19 HOW SUPPLIED/STORAGE AND HANDLING

Pfizer-BioNTech COVID-19 Vaccine Suspension for Intramuscular Injection, Multiple Dose Vials are supplied in a carton containing 25 multiple dose vials (NDC 59267-1000-3) or 195 multiple dose vials (NDC 59267-1000-2). After dilution, one vial contains 6 doses of 0.3 mL. Vial labels and cartons may state that after dilution, a vial contains 5 doses of 0.3 mL. The information in this Full EUA Prescribing Information regarding the number of doses per vial after dilution supersedes the number of doses stated on vial labels and cartons.

During storage, minimize exposure to room light, and avoid exposure to direct sunlight and ultraviolet light.

Do not refreeze thawed vials.

Frozen Vials Prior to Use

Cartons of Pfizer-BioNTech COVID-19 Vaccine Multiple Dose Vials arrive in thermal containers with dry ice. Once received, remove the vial cartons immediately from the thermal container and preferably store in an ultra-low temperature freezer between -80°C to -60°C (-112°F to -76°F) until the expiry date printed on the label. Alternatively, vials may be stored at -25°C to -15°C (-13°F to 5°F) for up to 2 weeks. Vials must be kept

Document Released Under the Access to Information Act

frozen and protected from light, in the original cartons, until ready to use. Vials stored at -25°C to -15°C (-13°F to 5°F) for up to 2 weeks may be returned one time to the recommended storage condition of -80°C to -60°C (-112°F to -76°F). Total cumulative time the vials are stored at -25°C to -15°C (-13°F to 5°F) should be tracked and should not exceed 2 weeks.

If an ultra-low temperature freezer is not available, the thermal container in which the Pfizer-BioNTech COVID-19 Vaccine arrives may be used as temporary storage when consistently re-filled to the top of the container with dry ice. Refer to the re-icing guidelines packed in the original thermal container for instructions regarding the use of the thermal container for temporary storage. The thermal container maintains a temperature range of -90°C to -60°C (-130°F to -76°F). Storage of the vials between -96°C to -60°C (-141°F to -76°F) is not considered an excursion from the recommended storage condition.

Transportation of Frozen Vials

If local redistribution is needed and full cartons containing vials cannot be transported at -90°C to -60°C (-130°F to -76°F), vials may be transported at -25°C to -15°C (-13°F to 5°F). Any hours used for transport at -25°C to -15°C (-13°F to 5°F) count against the 2-week limit for storage at -25°C to -15°C (-13°F to 5°F). Frozen vials transported at -25°C to -15°C (-13°F to 5°F) may be returned one time to the recommended storage condition of -80°C to -60°C (-112°F to -76°F).

Thawed Vials Before Dilution

Thawed Under Refrigeration

Thaw and then store undiluted vials in the refrigerator [2°C to 8°C (35°F to 46°F)] for up to 1 month. A carton of 25 vials or 195 vials may take up to 2 or 3 hours, respectively, to thaw in the refrigerator, whereas a fewer number of vials will thaw in less time.

Thawed at Room Temperature

For immediate use, thaw undiluted vials at room temperature [up to 25°C (77°F)] for 30 minutes. Thawed vials can be handled in room light conditions.

Vials must reach room temperature before dilution.

Undiluted vials may be stored at room temperature for no more than 2 hours.

Transportation of Thawed Vials

Available data support transportation of one or more thawed vials at 2°C to 8°C (35°F to 46°F) for up to 12 hours.

Vials After Dilution

After dilution, store vials between 2°C to 25°C (35°F to 77°F) and use within 6 hours from the time of dilution. During storage, minimize exposure to room light, and avoid exposure to direct sunlight and ultraviolet light. Any vaccine remaining in vials must be discarded after 6 hours. Do not refreeze.

20 PATIENT COUNSELING INFORMATION


Advise the recipient or caregiver to read the Fact Sheet for Recipients and Caregivers.

Revised: 19-Mayxx

The vaccination provider must include vaccination information in the state/local jurisdiction's Immunization Information System (IIS) or other designated system. Advise recipient or caregiver that more information about IISs can be found at: <https://www.cdc.gov/vaccines/programs/iis/about.html>.

21 CONTACT INFORMATION

For general questions, visit the website or call the telephone number provided below.

Website	Telephone number
www.cvdvaccine.com 	<p>1-877-829-2619 (1-877-VAX-CO19)</p>

This Full EUA Prescribing Information may have been updated. For the most recent Full EUA Prescribing Information, please see www.cvdvaccine.com.



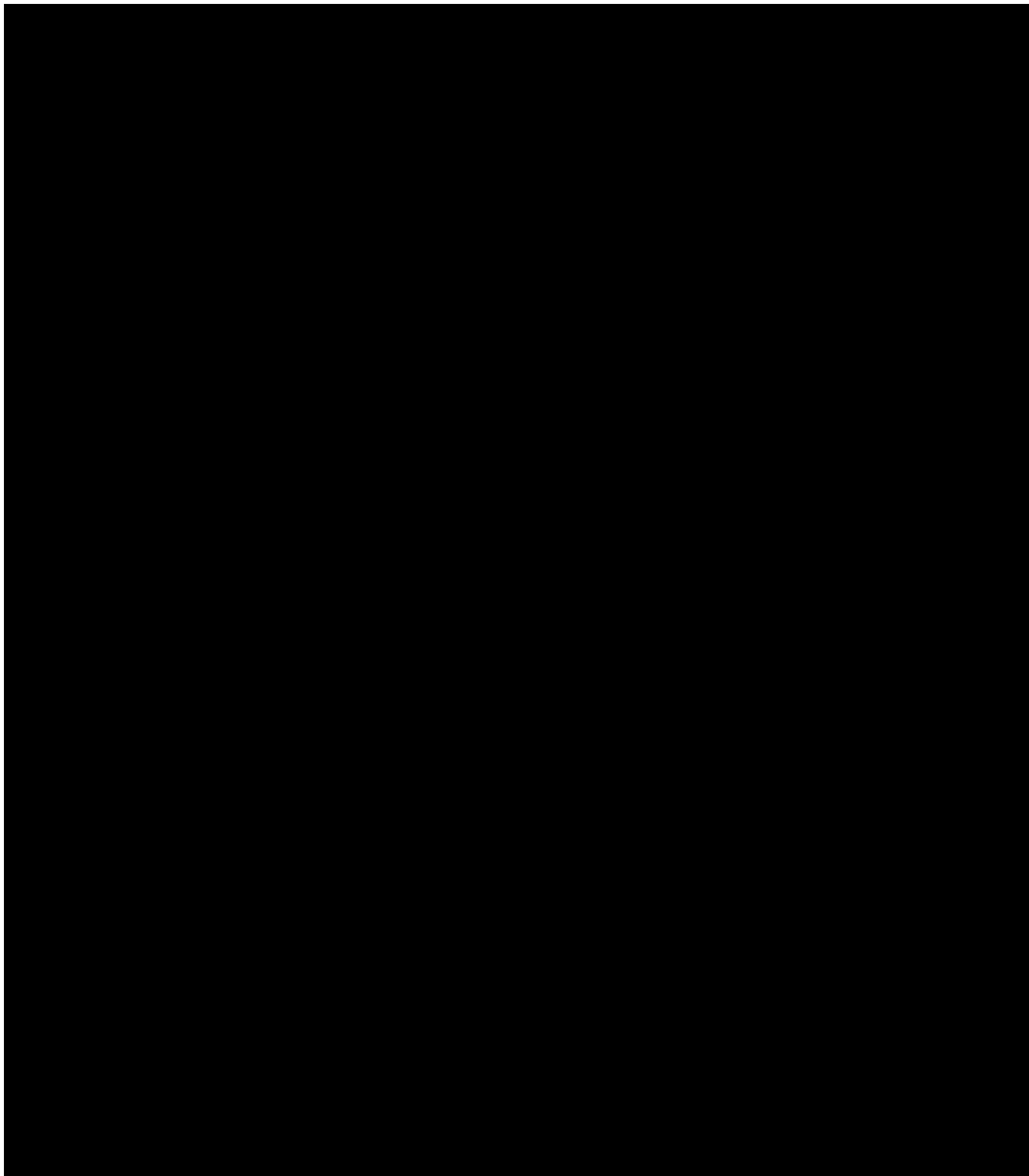
Manufactured by
Pfizer Inc., New York, NY 10017

BIONTECH

Manufactured for
BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz, Germany

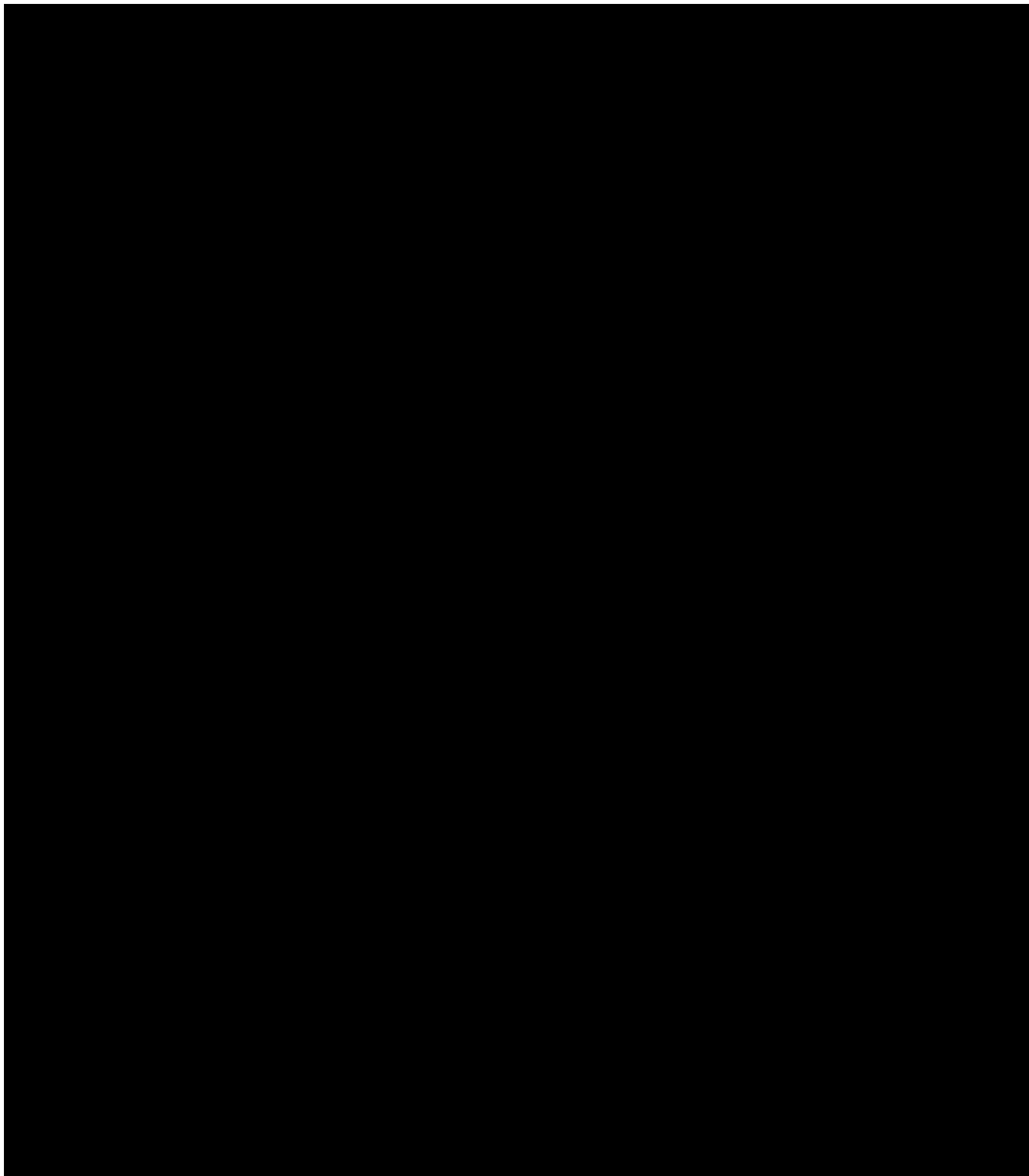
LAB-1457-8.2b

Revised: ~~19 May~~xx June 2021



[REDACTED]

[REDACTED]



[REDACTED]

[REDACTED]

From: Hunt, Melissa (HC/SC)
Sent: 2021-06-25 9:07 AM
To: Rose, Jhona (HC/SC); Faraci, Maria (HC/SC); Salem, Myriam (HC/SC)
Subject: FW: [EXTERNAL] Labelling text from US FDA
Attachments: EUA.27034.179_FS for Vaccination Providers-Full EUA PI_Final-5.19.2010 myocarditis pericarditis_CBER edits_6.25.2021.docx; EUA 27034.167_FS for Recipients and Caregivers_Final-5.10.2021 myocarditis pericarditis_CBER edits_6.25.2021.docx

Importance: High

Good Morning,

Please see the labelling from the U.S.. I understand there will be a meeting with BRDD at some point this morning for everyone to go over labelling and determine next steps.

Thanks!
Melissa

From: Lourenco, Celia (HC/SC) <celia.lourenco@canada.ca>
Sent: 2021-06-25 8:51 AM
To: Sabourin, Pierre (HC/SC) <pierre.sabourin@canada.ca>; Hardy, Stephanie (HC/SC) <stephanie.hardy@canada.ca>; Robinson2, Kelly (HC/SC) <kelly.robinson2@canada.ca>; Sommerer, Sophie (HC/SC) <sophie.sommerer@canada.ca>; Hunt, Melissa (HC/SC) <melissa.hunt@canada.ca>; Bouthillier, Leo (HC/SC) <leo.bouthillier@canada.ca>; Sharma, Supriya (HC/SC) <supriya.sharma@canada.ca>; Smith4, Melissa (HC/SC) <melissa.smith4@canada.ca>
Subject: Fwd: [EXTERNAL] Labelling text from US FDA

Bonjour, attached is the proposed labelling changes from US FDA on myocarditis, shared under confidentiality agreement for our consideration and next steps in updating labelling in Canada.

Bonne journée,

Celia

Sent from my iPhone

Begin forwarded message:

From: "[REDACTED]" <[REDACTED]@fda.hhs.gov>
Date: June 25, 2021 at 8:24:31 AM EDT
To: "Lourenco, Celia (HC/SC)" <celia.lourenco@canada.ca>

Cc: [REDACTED] (CBER)" [REDACTED]@fda.hhs.gov>
Subject: RE: [EXTERNAL] Labelling text

SHARING UNDER THE TERMS OF OUR MUTUAL
CONFIDENTIALITY AGREEMENT

Dear Celia,

Please see the latest version of the changes to the EUA documents for providers and patients incorporating the information on myocarditis/pericarditis. These are near-final.

Best Regards,

[REDACTED]

-----Original Message-----

From: Lourenco, Celia (HC/SC) <celia.lourenco@canada.ca>
Sent: Friday, June 25, 2021 6:11 AM
To: [REDACTED]@fda.hhs.gov>
Cc: [REDACTED] (CBER) [REDACTED]@fda.hhs.gov>
Subject: [EXTERNAL] Labelling text

CAUTION: This email originated from outside of the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.

Good morning [REDACTED]

Just following up on the labelling text for the mRNA vaccines and myocarditis / pericarditis. Health Canada would appreciate an advance copy of the text if possible.

With many thanks and best regards,

Celia

Celia Lourenco
Director General
Health Canada

Sent from my iPhone

Characterizing the incidence of adverse events of special interest for COVID-19 vaccines across eight countries: a multinational network cohort study

AUTHORS: Xintong Li^{1*}, Anna Ostropolets^{2*}, Rupa Makadia³, Azza Shaoibi³, Gowtham Rao³, Anthony G. Sena^{3,6}, Eugenia Martinez-Hernandez⁴, Antonella Delmestri¹, Katia Verhamme⁶, Peter R Rijnbeek⁶, Talita Duarte-Salles⁵, Marc Suchard^{7,8}, Patrick Ryan^{2,3}, George Hripcsak², Daniel Prieto-Alhambra^{1,6}

*Joint first authors

AFFILIATIONS:

1. Centre for Statistics in Medicine, NDORMS, University of Oxford, Oxford, United Kingdom
2. Department of Biomedical Informatics, Columbia University Irving Medical Center, New York, NY, USA
3. Janssen Research and Development, Titusville, NJ, USA
4. Neurology Department, Hospital Clinic de Barcelona and University of Barcelona, Barcelona, Spain
5. Fundacio Institut Universitari per a la recerca a l'Atencio Primaria de Salut Jordi Gol i Gurina (IDIAPJGol), Barcelona, Spain
6. Department of Medical Informatics, Erasmus University Medical Center, Rotterdam, The Netherlands
7. Department of Biostatistics, Fielding School of Public Health, University of California, Los Angeles, Los Angeles, CA USA,
8. Department of Human Genetics, David Geffen School of Medicine at UCLA, University of California, Los Angeles, UCLA, Los Angeles, CA, USA

Corresponding author:

Prof Daniel Prieto-Alhambra

Botnar Research Centre, Windmill Road, OX37LD, Oxford, United Kingdom

daniel.prietoalhambra@ndorms.ox.ac.uk

NOTE: This preprint reports new research that has not been certified by peer review and should not be used to guide clinical practice.

Summary (275 words)

Background

As large-scale immunization programs against COVID-19 proceed around the world, safety signals will emerge that need rapid evaluation. We report population-based, age- and sex-specific background incidence rates of potential adverse events of special interest (AESI) in eight countries using thirteen databases.

Methods

This multi-national network cohort study included eight electronic medical record and five administrative claims databases from Australia, France, Germany, Japan, Netherlands, Spain, the United Kingdom, and the United States, mapped to a common data model. People observed for at least 365 days before 1 January 2017, 2018, or 2019 were included. We based study outcomes on lists published by regulators: acute myocardial infarction, anaphylaxis, appendicitis, Bell's palsy, deep vein thrombosis, disseminated intravascular coagulation, encephalomyelitis, Guillain-Barre syndrome, hemorrhagic and non-hemorrhagic stroke, immune thrombocytopenia, myocarditis/pericarditis, narcolepsy, pulmonary embolism, and transverse myelitis. We calculated incidence rates stratified by age, sex, and database. We pooled rates across databases using random effects meta-analyses. We classified meta-analytic estimates into Council of International Organizations of Medical Sciences categories: very common, common, uncommon, rare, or very rare.

Findings

We analysed 126,661,070 people. Rates varied greatly between databases and by age and sex. Some AESI (e.g., myocardial infarction, Guillain-Barre syndrome) increased with age, while others (e.g., anaphylaxis, appendicitis) were more common in young people. As a result, AESI were classified differently according to age. For example, myocardial infarction was very rare in children, rare in women aged 35-54 years, uncommon in men and women aged 55-84 years, and common in those aged ≥85 years.

Interpretation

We report robust baseline rates of prioritised AESI across 13 databases. Age, sex, and variation between databases should be considered if background AESI rates are compared to event rates observed with COVID-19 vaccines.

MAIN TEXT (2947 words)

Introduction

On 11 March 2020, the World Health Organization (WHO) declared the outbreak of COVID-19, caused by the SARS-CoV-2 virus, a global pandemic. As of March 2021, over 100 million confirmed cases and 2.7 million deaths have been reported worldwide.¹ Vaccines for COVID-19 have been developed at unprecedented speed, with phase 3 clinical efficacy trials reporting results for some vaccines less than a year after the WHO declared the pandemic. Several vaccines have been authorised by regulators since December 2020, such as the European Medicines Agency (EMA), the Food and Drug Administration (FDA) in the US, and the UK Medicines and Healthcare Products Regulatory Agency (MHRA). Large-scale immunization programs are ongoing worldwide.

While this scientific achievement should be celebrated, we must recognize that emergency use is accompanied by residual uncertainty about the safety and effectiveness of vaccines in all populations of interest. As with all medical products reaching the milestone of regulatory authorization, vaccine safety must continue to be monitored to complement what was initially learned during clinical development. Spontaneous adverse event reporting has served as a foundational component of post-approval pharmacovigilance activities to ensure the safe and appropriate use of medical products. Observational healthcare data captured during the routine course of clinical care, such as electronic health records and administrative claims, can augment pharmacovigilance by providing real-world context about potential adverse events and their rates in populations of interest. Background rates of adverse events have historically played an important role in monitoring the safety of vaccines by serving as a baseline comparator for observed rates among those vaccinated.^{2,3} Each new vaccine has potential adverse events of special interest (AESI) that warrant focused evaluation, based on historical precedent set by prior vaccines and knowledge acquired during its development.

As COVID-19 vaccines have received authorization for emergency use, regulatory agencies around the world have been preparing safety surveillance strategies. The US FDA Center for Biologics Evaluation and Research published a protocol on “Background Rates of Adverse Events of Special Interest for COVID-19 Vaccine Safety Monitoring.”⁴ The European Medicines Agency-funded vACCine covid-19 monitoring readinESS (ACCESS) project also included estimation of background AESI rates in their protocol.⁵ Recognizing the global burden that COVID-19 represents and following the WHO Council for International Organizations of Medical Sciences (CIOMS) guidance that the most valid data for comparison in a particular area are the background rates from the local population,⁶ the Observational Health Data Sciences and Informatics (OHDSI) community collaborated to design and execute an international open science study to characterize background rates of COVID-19 AESI. In this paper, we provide descriptive epidemiology context for COVID-19 AESIs using observational data from Australia, France, Germany, Japan, Netherlands, Spain, the UK, and the US.

Methods

Study design

A multinational, multi-database population-based network cohort study.

Data sources

We included thirteen databases from eight countries, of which eight were electronic health record data sources and five were administrative claims data sources.

The electronic health record databases were: 1. IQVIA Australia Electronic Medical Records (IQVIA_AUSTRALIA); 2. Integrated Primary Care Information (IPCI_NETHERLANDS), a primary care records database from the Netherlands; 3. IQVIA Longitudinal Patient Data France (IQVIA_FRANCE); 4. IQVIA Disease Analyser Germany (IQVIA_GERMANY); 5. Information System for Research in Primary Care (SIDIAP_H_SPAIN), a primary care records database that covers over 80% of the population of Catalonia, Spain; 6. Clinical Practice Research Datalink, which consists of data collected from UK primary care for all ages (CPRD_GOLD_UK); 7. Columbia University Irving Medical Center (CUMC_US), which covers the New York-Presbyterian Hospital/Columbia University Irving Medical Center in the US; and 8. Optum® de-identified Electronic Health Record Dataset (OPTUM_EHR_US), which covers more than 103 million patients and over 7,000 hospitals and clinics across the US.

The claims-based databases were the Japan Medical Data Center (JMDC_JAPAN) and four US administrative claims databases: IBM MarketScan Commercial Claims and Encounters Database (CCAE_US), IBM MarketScan Medicare Supplemental and Coordination of Benefits Database (MDCR_US), IBM MarketScan Multi-State Medicaid Database (MDCD_US), Optum® De-Identified Clinformatics® Data Mart Database – Socio-Economic Status (OPTUM_SES_US).

A detailed description of the databases can be found in Appendix Table 1.

All datasets were previously mapped to the Observational Medical Outcomes Partnership common data model, which is maintained by the Observational Health Data Sciences and Informatics (OHDSI) network. The analysis code could therefore be distributed across all contributing centers without sharing patient-level data.^{7,8}

Population/study participants

In our primary analysis, we defined the target at-risk population as people who were observed on 1 January 2017, 1 January 2018, or 1 January 2019 and were observed for at least 365 days before this observation date. We defined 1 January each year as the index date.

Events of interest

The events of interest in this study were the AESIs that might need evaluation following COVID-19 vaccination. This outcome list was developed primarily based on the “Background Rates of Adverse Events of Special Interest for COVID-19 Vaccine Safety Monitoring” protocol published by the FDA Center for Biologics Evaluation and Research, the prioritized COVID-19 vaccine AEFI list by the Brighton Collaboration, and other previous studies.^{4,9} Fifteen events were included: non-hemorrhagic stroke, hemorrhagic stroke, acute myocardial infarction, deep vein thrombosis, pulmonary embolism, anaphylaxis, Bell’s palsy, myocarditis/pericarditis, narcolepsy, appendicitis, immune thrombocytopenia, disseminated intravascular coagulation, encephalomyelitis (including acute disseminated encephalomyelitis), Guillain-Barre syndrome, and transverse myelitis.⁴

Events were identified by condition occurrence records (e.g., diagnosis codes from claims or diagnosis codes and problem lists from electronic health records). Encephalomyelitis, non-hemorrhagic stroke, hemorrhagic stroke, and acute myocardial infarction definitions also required the record to occur within an inpatient setting (any position), while the Guillain-Barre syndrome definition required the condition to be recorded in an inpatient setting in the primary position.

Qualifying events could not be previously observed in a ‘clean window’ period before the index date. In keeping with the FDA protocol, we applied a clean window of 365 days for all events except anaphylaxis (30 days) and facial nerve palsy and encephalomyelitis (183 days).⁴ The full specifications of all phenotype definitions, including source codes and standard

concepts, are available in Appendix Tables 2 and 3.

As the CPRD-GOLD (UK), IQVIA (France, Germany, and Australia), and IPCI (the Netherlands) databases only included primary care data, we did not use them for events whose definition required an inpatient diagnosis.

Analysis

We defined the time-at-risk as a 365-day period following the index date. People contributed time-at-risk from 1 January to 31 December for each qualifying year in 2017 to 2019, but time was censored during the clean window following an event and at the end of a person's observation period. One person could contribute more than one event, with outcome-specific pre-specified clean periods of 30 to 365 days used to avoid duplicate counts.

Incidence rates were estimated as the total number of events divided by the person-time at risk per 100,000 person-years. We calculated the age-by-sex specific incidence rates in each database and report all rates where the event counts exceeded a minimum cell count of 5. Age was calculated as year of index date minus year of birth and was partitioned into eight mutually exclusive age groups: 1-5 years old, 6-17, 18-35, 36-55, 56-64, 65-74, 75-84, and 85 years and older. We then pooled age-sex specific rates of each AESI across all databases using random-effects models with the DerSimonian-Laird method to estimate between-database variance.¹⁰ We estimated 95% predicted intervals (95% confidence intervals) using the R package 'meta'.¹¹

Meta-analytic age and sex-specific rates were classified using the World Health Organization Council for International Organizations of Medical Sciences (CIOMS) thresholds: very common ($\geq 1/10$), common ($< 1/10$ to $\geq 1/100$), uncommon ($< 1/100$ to $\geq 1/1,000$), rare ($< 1/1,000$ to $\geq 1/10,000$), and very rare ($< 1/10,000$).¹²

All statistical analyses were performed in R software.¹³ The study protocol and analysis code are available at: <https://github.com/ohdsi-studies/Covid19VaccineAesiIncidenceCharacterization>

Ethical approval

The protocol for this research was approved by the Independent Scientific Advisory Committee (ISAC) for MHRA Database Research (protocol number 20_000211), the IDIAPJGOL Clinical Research Ethics Committee (project code: 21/007-PCV), the IPCI governance board (application number 3/2021), and the Columbia University Institutional Review Board (AAO7805).

Results

From 13 databases, 126,661,070 people contributed 227,043,370 person-years of follow-up. Each database captured important different population demographics, as shown in Table 1, and collectively represented all age and sex subgroups from eight countries.

Table 2 summarises the incidence rates of the 15 AESIs, stratified by age and sex, based on prediction intervals from a meta-analysis of the database estimates. Each age/sex subgroup was also classified using the CIOMS adverse event frequency system (very common, common, uncommon, rare, or very rare). The incidence of several outcomes varied substantially by age. For example, acute myocardial infarction was very rare ($< 1/10,000$) in women under 35 years, rare ($1/1,000$ to $1/10,000$) in women aged 35 to 54 years, uncommon ($1/100$ to $1/1,000$) in both men and women aged 55 to 84 years, and common ($1/10$ to $1/100$) in men and women aged 85 years and older. For both men and women, deep vein thrombosis was rare in those

under 18 years, uncommon in those aged 35 to 84 years, and common in those 85 years and older. Women aged 18 to 34 years had a higher rate of deep vein thrombosis than men of the same age.

The AESIs studied spanned the continuum of possible frequencies. Non-hemorrhagic stroke, acute myocardial infarction, and deep vein thrombosis were all common in those aged 85 years and older and uncommon in those aged 55 to 74 years. Anaphylaxis, Bell's palsy, appendicitis, and immune thrombocytopenia were largely rare in all age groups, although appendicitis was uncommon in those aged 6 to 34 years. Guillain-Barre syndrome and transverse myelitis were very rare in nearly all subgroups.

The prediction intervals for each age-sex subgroup were notably wide, reflecting the substantial population-level heterogeneity observed across sources. Figure 1 shows the database-specific incidence rates that were used to calculate the meta-analytic estimates. The rates recorded for deep vein thrombosis highlight this variation. For women aged 35 to 54 years, the incidence rates ranged from 159/100,000 person-years in Spain (SIDIAP) to 866/100,000 person-years in the US (MDCD). We obtained 13 database estimates for the incidence in women aged 65 to 74 years, ranging from 387/100,000 to 1,443/100,000 person-years. Eight databases gave rates under 650/100,000 person-years (CPRD-GOLD in the UK; CUIMC in the US; IPCI in the Netherlands; IQVIA in Australia, France, and Germany; JMDC in Japan; and SIDIAP-H in Spain), while three databases gave rates more than twice as high, at over 1,300/100,000 person-years (MDCD, MDCR, and OPTUM-SES in the US). Among women aged 75 to 84 years, the lowest incidence rate was 585/100,000 person-years (CPRD-GOLD in the UK) and the highest was 2,167/100,000 person-years (MDCR in the US). We could not find any consistent patterns to explain which databases yielded higher or lower rates across outcomes. Appendix Table 4 lists all database-specific incidence rates.

Discussion

To our knowledge, this is the largest study to date on the descriptive epidemiology of the AESIs prioritised for post-marketing surveillance of COVID-19 vaccines. We report background rates of deep vein thrombosis, pulmonary embolism, stroke, immune thrombocytopenia, and disseminated intravascular coagulation, which are particularly relevant for COVID-19 vaccines given the observed effects of the SARS-COV-2 virus on coagulopathy.¹⁴⁻¹⁷

Our study provides a comprehensive, detailed assessment of the incidence rates of 15 AESIs across 13 databases, eight countries, and four continents. We found considerable heterogeneity between geographies and databases, suggesting that caution is needed when interpreting the difference between any observed and expected rates. We observed considerable variability with age and sex, emphasizing the need for standardization if background rates are used for surveillance purposes.

Many countries and organizations, such as the US and EU, have passive spontaneous adverse event reporting systems, such as the Vaccine Adverse Event Reporting System (VAERS). However, these systems cannot be used to calculate epidemiological estimates of the burden of disease, including incidence rates, because they lack denominators, which are the total number of persons or person-times being observed.^{18,19} Background incidence rates have been used to estimate the expected number of events in the general population.^{3,19} They are often obtained from the literature, but methods, case and population definitions, data, and calendar time can vary across publications. In contrast, we calculated all of the presented estimates using precisely the same setting and common analysis procedures, phenotyping algorithms, and data model. However, we still found substantial heterogeneity, suggesting that using a single overall estimate inadequately represents the true uncertainty around event

incidence and may lead to confusion.

Population-level heterogeneity across data sources was substantial for all events, even after standardizing outcome definitions and stratifying by age and sex. While potentially concerning when seen together in one analysis, our findings are consistent with what has been observed in the literature. For example, in our study, the meta-analysis estimated incidence rates of transverse myelitis ranging from 1 to 4 per 100,000 person-years depend on age-sex strata. Previous studies have reported overall incidence rates of transverse myelitis ranging from 0.4 to 4.6 per 100,000 person-years.^{19,20} The rates of Bell's palsy among those over 65 years old has ranged from 4.6 per 100,000 person-years in European data to 174 per 100,000 person-years in US data.^{21,22} Rates of narcolepsy from 1 to over 30 per 100,000 person-years have been reported among those aged 25 to 44 years.^{21,22} Recently reported data from the ACCESS project also showed heterogeneity in background rates.⁵ This heterogeneity needs to be taken into account when comparing rates across populations.

Most of the studied outcomes also had considerable within-source patient-level heterogeneity that followed age and sex patterns. For example, rates of cardiovascular diseases such as acute myocardial infarction, hemorrhagic and non-hemorrhagic stroke, deep vein thrombosis, and pulmonary embolism increased with age. The incidence of Guillain-Barre syndrome and Bell's palsy also increased with age. Narcolepsy and appendicitis were more common in younger populations. The patterns observed in our study were generally comparable with previous reports.^{2,3,21-25} Stratification by age and sex or standardization are likely to be useful analytic strategies to reduce confounding when comparing incidence rates across populations. However, the magnitude of heterogeneity across sources within age-sex subgroups suggest that residual patient-level differences will remain, including the differences in the distributions of other risk factors such as comorbidities and medication use.

Comparing published results can be limited by differing study methodology, including the time-at-risk definition, study period, event definitions, population coverage, calendar year, and geographic location.²⁶ Different subgroup definitions also make direct comparison difficult. For example, previous studies of Guillain-Barre syndrome have used age strata that do not fully overlap with each other.^{2,5,21,25,27,28} In contrast, because we applied the same definitions, data model, and analysis to all of the databases within our study, the heterogeneity observed cannot be attributed to analysis variability. Instead, it may have been due to differences in the underlying populations, healthcare systems, and data capture processes. Although some variability may have been due to systematic error, selection bias or differential outcome measurement error between databases, some may reflect true population differences such as socioeconomic status and comorbidities.

As we observed notable differences between age, sex, and databases, caution should be exercised when using incidence rates as a basis for comparison. Comparisons between incidence rates from different sources may be subject to substantial systematic error. We observed large variations between electronic health records and claims data sources when using the same analysis and outcome definitions. Comparisons with rates derived from randomised trials or spontaneous reporting data may have even greater variability. If observational databases are to be used to inform safety surveillance activities, within-database analyses (such as self-controlled case designs or propensity-score adjusted comparative cohort designs) may help reduce study bias for any given comparison. Demonstrating consistent effects across databases may further strengthen confidence in results. If observational data are used to derive historical 'expected' rates and compared against observed rates of events from another source, then the uncertainty in the background rate must be appropriately integrated to avoid misleading conclusions.

Our large number of participating databases, geographical coverage, and sizable study

population allowed us to provide a comprehensive assessment of the background incidence rates across different healthcare systems and regions across the globe. Our study took advantage of the Observational Medical Outcomes Partnership common data model, which allowed us to use the same study design and analytical code and to gather results from participating data partners rapidly and without transferring patient-level data. All outcome definitions, clinical codes and phenotype algorithms have been made open source and are available online for review and to maximise reproducibility and reuse.

The primary limitation of this study is that all outcomes may have been subject to measurement error. As the outcome definitions were based on the presence of specific diagnostic codes and were not validated further, they may have had imperfect sensitivity or specificity. The analysis relied on data from 2017 to 2019 using a target population of all people in each database with >365 days of observation indexed on 1 January, 365 days' time-at-risk, and outcome-specific clean windows to allow for recurrent events. The impact of these design decisions should be explored further.

Conclusion

This study comprehensively assessed the descriptive epidemiology of potential AESIs for COVID-19 vaccines. It highlighted the wide range of adverse effects being monitored, from very rare neurological disorders to more common thromboembolic conditions. We reported large variations in the observable rates of AEFI by age group and sex, demonstrating the need to account for stratification or standardization before using background rates for safety surveillance. We also found significant population-level heterogeneity in AEFI rates between databases, implying that individual study estimates should be interpreted with caution and systematic error associated with database choice should be incorporated into any analysis. These background rates should provide useful real-world context to inform public health efforts aimed at ensuring patient safety while promoting the appropriate use of vaccines worldwide.

Tables & Figures

Table 1: Demographics of the included populations, stratified by database

	CCAE_US	MDCD_US	MDCR_US	OPTUM_EHR_US	OPTUM_SES_US	CUMC_US	CPRD_GOLD_UK	IPCI_NETHERLANDS	SIDIAP_H_SPAIN	IQVIA_FRANCE	IQVIA_GERMANY	IQVIA_AUSTRALIA	JMDC_JAPAN
Total patients	25,315,777	12,966,011	1,533,709	40,955,085	18,643,608	1,164,196	4,532,766	1,536,283	2,217,536	1,746,371	9,295,525	252,212	6,501,991
Person-years	42,889,550	23,203,712	2,484,782	72,328,897	32,474,685	2,174,312	9,638,136	3,326,570	5,497,613	3,008,350	16,784,613	383,668	12,848,482
Age													
1 - 5	4.96%	13.54%	0.0%	4.52%	3.36%	3.49%	5.42%	5.13%	4.5%	5.69%	3.32%	5.32%	6.37%
6 - 17	16.28%	32.3%	0.0%	11.65%	10.36%	9.06%	14.01%	13.74%	11.73%	15.38%	8.86%	12.6%	16.06%
18 - 34	25.26%	22.26%	0.0%	19.98%	17.87%	17.1%	20.87%	19.85%	16.91%	18.83%	15.19%	20.22%	23.59%
35 - 54	31.98%	15.48%	0.0%	26.22%	23.54%	25.84%	26.86%	25.7%	29.92%	25.58%	25.16%	27.7%	35.84%
55 - 64	18.63%	7.75%	0.0%	16.25%	12.79%	15.77%	13.11%	14.32%	13.01%	13.11%	17.0%	14.4%	13.54%
65 - 74	2.88%	4.88%	47.8%	11.79%	16.66%	14.77%	10.36%	11.75%	11.13%	11.33%	13.76%	10.81%	4.3%
75 - 84	0.0%	2.63%	35.01%	6.48%	10.65%	9.52%	6.4%	6.79%	8.16%	6.7%	12.82%	6.07%	0.32%
85+	0.0%	1.16%	17.19%	3.11%	4.77%	4.44%	2.96%	2.71%	4.64%	3.38%	3.9%	2.86%	0.0%
Sex													
Female	51.5%	56.47%	55.38%	56.7%	51.47%	59.54%	50.47%	51.01%	50.52%	53.03%	57.45%	54.4%	45.01%
Male	48.5%	43.53%	44.62%	43.3%	48.53%	40.46%	49.53%	48.99%	49.48%	46.97%	42.55%	45.6%	54.99%

*CCAE_US: IBM MarketScan Commercial Claims and Encounters Database, CPRD_GOLD_UK: Clinical Practice Research Datalink, CUMC_US: Columbia University Irving Medical Center, IPCI_NETHERLANDS: Integrated Primary Care Information, IQVIA_AUSTRALIA: IQVIA Australia Electronic Medical Records, IQVIA_FRANCE: IQVIA Longitudinal Patient Data France, IQVIA_GERMANY: IQVIA Disease Analyser Germany, JMDC_JAPAN: Japan Medical Data Center, MDCD_US: IBM MarketScan Multi-State Medicaid Database, MDCR_US: IBM MarketScan Medicare Supplemental and Coordination of Benefits Database, OPTUM_EHR_US: Optum® de-identified Electronic Health Record Dataset, OPTUM_SES_US: Optum® De-Identified Clinformatics® Data Mart Database – Socio-Economic Status, SIDIAP_H_SPAIN: Information System for Research in Primary Care – Hospitalization Linked Data

Table 2. Pooled estimated age-sex stratified incidence rates per 100,00 person-years (with 95% confidence intervals), calculated from meta-analyses.

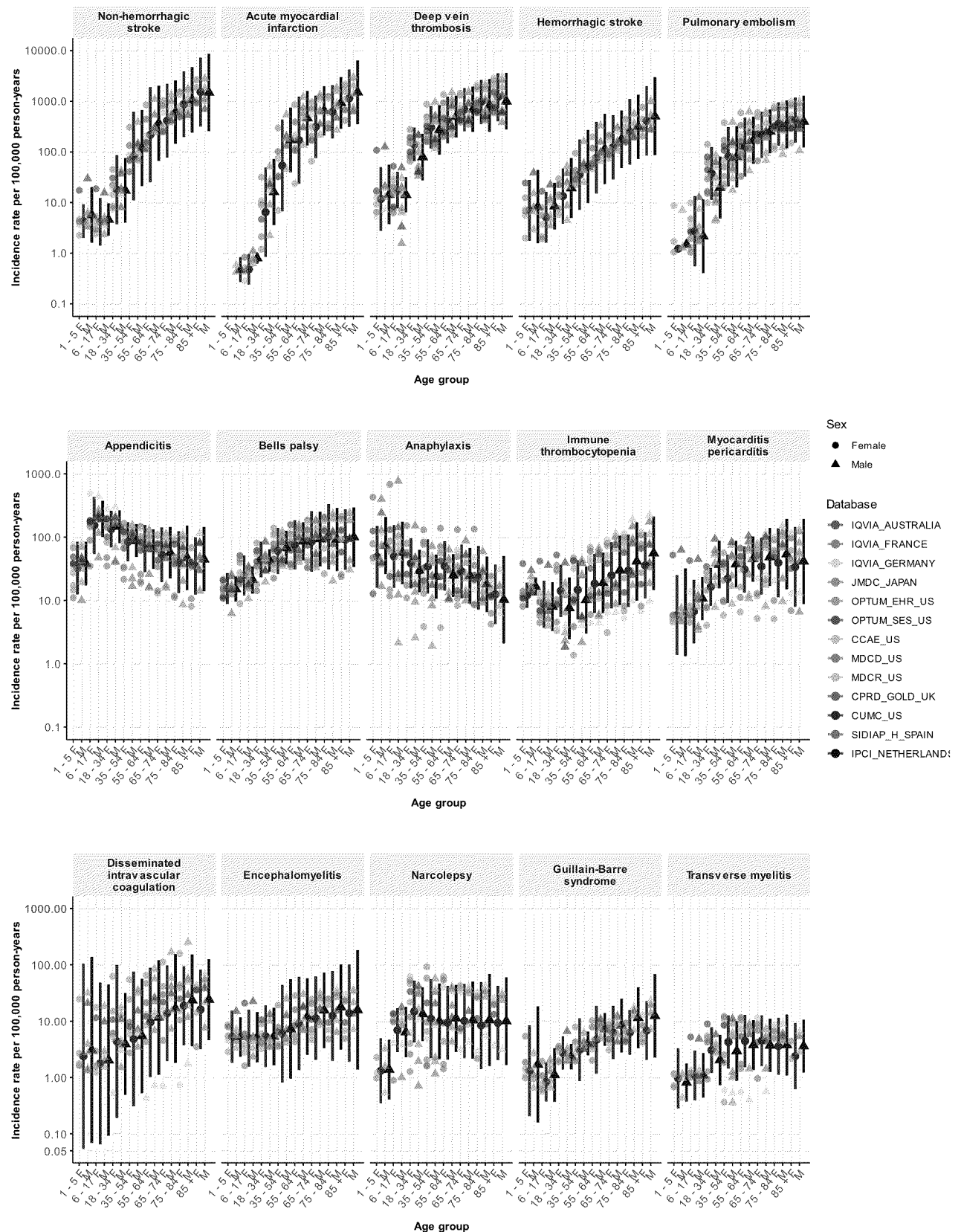
Incidence rate (per 100,000 person-years) by age group									
Outcome	Sex	1 - 5	6 - 17	18 - 34	35 - 54	55 - 64	65 - 74	75 - 84	85+
Non-hemorrhagic stroke	Female	4 (2-9)	4 (1-12)	18 (4-86)	83 (11-617)	217 (25-1882)	413 (77-2198)	874 (197-3884)	1523 (320-7239)
	Male	6 (2-20)	5 (2-10)	17 (4-75)	119 (21-664)	370 (67-2046)	612 (145-2578)	1063 (242-4662)	1495 (260-8607)
Acute myocardial infarction	Female	<1 (<1-1)	<1 (<1-1)	6 (1-49)	54 (7-430)	171 (24-1235)	312 (76-1280)	617 (184-2069)	1144 (313-4184)
	Male	<1 (<1-1)	1 (1-1)	16 (4-72)	172 (40-740)	467 (135-1611)	653 (214-1994)	934 (290-3013)	1514 (356-6432)
Deep vein thrombosis	Female	12 (3-50)	18 (8-40)	140 (66-298)	306 (117-797)	428 (150-1224)	683 (257-1820)	975 (360-2642)	1206 (407-3572)
	Male	14 (4-55)	14 (6-32)	80 (28-228)	272 (88-836)	499 (194-1289)	695 (250-1931)	831 (254-2720)	1003 (278-3616)
Hemorrhagic stroke	Female	7 (2-28)	5 (2-16)	13 (4-47)	36 (7-175)	77 (15-389)	124 (29-527)	249 (56-1108)	412 (85-1986)
	Male	8 (2-43)	8 (3-24)	19 (5-76)	51 (10-268)	115 (23-562)	178 (49-650)	312 (73-1340)	506 (86-2961)
Pulmonary embolism	Female	1 (<1-36)	3 (1-13)	38 (11-124)	81 (21-309)	125 (33-470)	217 (77-611)	358 (135-951)	427 (154-1184)
	Male	1 (<1-24)	2 (<1-12)	20 (5-80)	80 (20-318)	171 (59-497)	256 (96-683)	349 (119-1030)	398 (124-1277)
Appendicitis	Female	32 (12-84)	154 (55-430)	134 (69-260)	85 (42-172)	66 (28-156)	53 (20-143)	40 (13-124)	35 (12-98)
	Male	38 (17-85)	194 (101-372)	146 (81-266)	88 (49-159)	65 (32-132)	57 (23-144)	47 (15-152)	45 (14-143)
Bells palsy	Female	15 (9-27)	25 (12-51)	44 (23-84)	61 (26-140)	76 (31-184)	86 (29-256)	101 (31-330)	92 (31-274)
	Male	15 (10-24)	21 (13-34)	43 (29-64)	68 (37-125)	86 (43-172)	94 (35-252)	92 (29-291)	100 (34-292)
Anaphylaxis	Female	49 (16-150)	50 (16-154)	39 (16-95)	34 (13-91)	35 (14-85)	29 (11-76)	23 (7-73)	12 (4-36)
	Male	74 (26-209)	56 (18-175)	29 (14-63)	24 (11-53)	25 (11-53)	24 (9-68)	18 (7-49)	10 (2-50)
Immune thrombocytopenia	Female	12 (8-19)	9 (4-21)	14 (6-36)	15 (5-43)	18 (6-53)	25 (8-82)	30 (8-110)	36 (11-118)
	Male	17 (12-23)	8 (3-19)	8 (2-23)	10 (3-35)	19 (6-57)	30 (9-105)	41 (10-170)	56 (15-210)
Myocarditis pericarditis	Female	6 (1-25)	7 (2-21)	16 (8-32)	22 (9-53)	31 (13-72)	35 (12-97)	39 (11-138)	34 (8-143)
	Male	7 (1-32)	11 (5-24)	37 (16-88)	37 (16-87)	45 (20-102)	49 (17-139)	54 (15-193)	41 (9-193)
Disseminated intravascular coagulation	Female	2 (<1-104)	2 (<1-48)	4 (<1-99)	5 (<1-75)	10 (1-89)	14 (2-97)	19 (4-94)	16 (3-82)
	Male	3 (<1-137)	2 (<1-44)	4 (<1-31)	5 (1-56)	12 (1-120)	17 (2-154)	23 (4-152)	24 (5-126)
Encephalomyelitis	Female	5 (2-15)	5 (2-16)	5 (2-19)	6 (1-44)	9 (1-61)	11 (2-62)	12 (2-77)	14 (2-100)
	Male	5 (2-12)	5 (2-14)	5 (2-17)	7 (1-55)	12 (3-58)	16 (3-73)	18 (3-101)	16 (1-180)
Narcolepsy	Female	1 (<1-5)	7 (3-17)	15 (4-52)	11 (2-55)	9 (2-42)	10 (2-46)	8 (1-49)	9 (2-42)
	Male	1 (<1-5)	6 (2-18)	13 (4-40)	10 (2-47)	11 (3-44)	10 (2-50)	10 (2-68)	10 (2-60)
Guillain-Barre syndrome	Female	1 (<1-8)	1 (<1-2)	3 (1-5)	3 (1-11)	5 (1-18)	6 (2-19)	6 (3-16)	7 (2-22)
	Male	2 (<1-18)	1 (<1-3)	2 (1-4)	4 (2-7)	7 (4-14)	8 (3-25)	11 (3-40)	12 (2-68)
Transverse myelitis	Female	1 (<1-3)	1 (<1-3)	3 (1-8)	4 (1-12)	4 (2-13)	4 (2-13)	4 (1-11)	2 (1-9)
	Male	1 (<1-2)	1 (<1-3)	2 (1-6)	3 (1-10)	4 (1-10)	4 (1-11)	4 (1-13)	4 (1-11)

CIOMS Frequency classification

Very rare: <1/10,000
Rare: >1/10,000 AND <1/1,000
Uncommon: >1/1,000 AND <1/100
Common: >1/100 AND <1/10
Very common: >1/10

*CIOMS: Council of International Organizations of Medical Sciences

Figure 1: Age-sex stratified incidence rates, overall and per database, for 15 adverse events of special interest



Contributors

DAP, XL, PR, and GH conceived the idea of this study. XL, AO, GH, PR, and DAP were responsible for interpreting the results and writing the manuscript. RM, AZ, GR, and AS were responsible for implementing the study. XL, AO, PR, RM, KV, PRR, TDS, and MAS Contributed to the study execution (Data holders). XL, AO, GH, and PR Contributed to the study design. All the co-authors contributed to writing the manuscript. All authors approved the final version and had final responsibility for the decision to submit for publication.

Declaration of interests

DPA's research group has received research grants from the European Medicines Agency, from the Innovative Medicines Initiative, from Amgen, Chiesi, and from UCB Biopharma; and consultancy or speaker fees from Astellas, Amgen and UCB Biopharma. GH and AO receive funding from the US National Institutes of Health and the US Food and Drug Administration. KV and PR work for a research group who receives/received unconditional research grants from Yamanouchi, Pfizer-Boehringer Ingelheim, Novartis, GSK, Amgen, Chiesi none of which relates to the content of this paper. PBR, RM, AS, GR, AGS are employee of Janssen Research and Development, and shareholder in Johnson & Johnson. MAS receives grants and contracts from the US Food & Drug Administration and the US Department of Veterans Affairs within the scope of this research, and grants and contracts from the US National Institutes of Health, IQVIA and Private Health Management outside the scope of this research. Funders had no role in the conceptualization, design, data collection, analysis, decision to publish nor preparation of the manuscript. TDS has no conflicts of interest to declare. EM has no conflicts of interest to declare.

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Data sharing

Patient-level data cannot be shared without approval from data custodians due to local information governance and data protection regulations. Aggregated data, analytical code, and detailed definitions of algorithms for identifying the events are available in a GitHub repository (<https://github.com/ohdsi-studies/Covid19VaccineAesilIncidenceCharacterization>).

Supplement materials

Appendix Table 1: database information

Appendix Table 2: adverse events of special interest phenotype definition and links

Appendix Table 3: source clinical codes used in phenotype definition

Appendix Table 4: age-sex specific crude incidence rates for each events of each database

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